(54) **Benzothiophene compounds, intermediates, compositions and methods**

(57) The present invention provides pharmaceutically active compounds of formula I
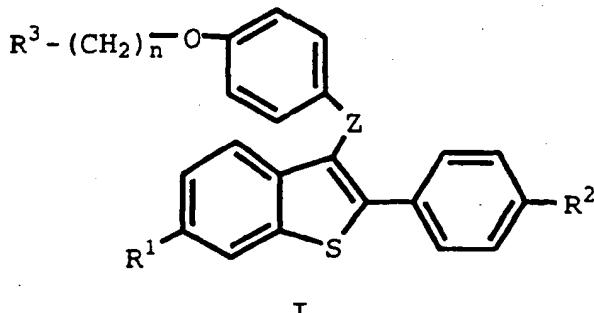
I

wherein

R^1 is -H, -OH, -O(C$_1$-C$_4$ alkyl), -OCOC$_6$H$_5$, -OCO(C$_1$-C$_6$ alkyl), or -OSO$_2$(C$_2$-C$_6$ alkyl);
R^2 is -H, -OH, -O(C$_1$-C$_4$ alkyl), -OCOC$_6$H$_5$, -OCO(C$_1$-C$_6$ alkyl), -OSO$_2$(C$_2$-C$_6$ alkyl), or halo;
R^3 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, di-
ethylamino, diisopropylamino, or 1-hexamethyleneimino;
n is 2 or 3; and
z is -O- or -S-;

or a pharmaceutically acceptable salt thereof.

Further provided are pharmaceutical compositions of compounds of formula I.

Description

[0001] This invention relates to the fields of pharmaceutical and organic chemistry and provides novel benzothiophene compounds which are useful for the treatment of the various medical indications associated with post-menopausal syndrome, and uterine fibroid disease, endometriosis, and aortal smooth muscle cell proliferation. The present invention further relates to intermediate compounds useful for preparing the pharmaceutically active compounds of the present invention, and pharmaceutical compositions.

[0002] "Post-menopausal syndrome" is a term used to describe various pathological conditions which frequently affect women who have entered into or completed the physiological metamorphosis known as menopause. Although numerous pathologies are contemplated by the use of this term, three major effects of post-menopausal syndrome are the source of the greatest long-term medical concern: osteoporosis, cardiovascular effects such as hyperlipidemia, and estrogen-dependent cancer, particularly breast and uterine cancer.

[0003] Osteoporosis describes a group of diseases which arise from diverse etiologies, but which are characterized by the net loss of bone mass per unit volume. The consequence of this loss of bone mass and resulting bone fracture is the failure of the skeleton to provide adequate structural support for the body. One of the most common types of osteoporosis is that associated with menopause. Most women lose from about 20% to about 60% of the bone mass in the trabecular compartment of the bone within 3 to 6 years after the cessation of menses. This rapid loss is generally associated with an increase of bone resorption and formation. However, the resorptive cycle is more dominant and the result is a net loss of bone mass. Osteoporosis is a common and serious disease among post-menopausal women.

[0004] There are an estimated 25 million women in the United States, alone, who are afflicted with this disease. The results of osteoporosis are personally harmful and also account for a large economic loss due its chronicity and the need for extensive and long term support (hospitalization and nursing home care) from the disease sequelae. This is especially true in more elderly patients. Additionally, although osteoporosis is not generally thought of as a life threatening condition, a 20% to 30% mortality rate is related with hip fractures in elderly women. A large percentage of this mortality rate can be directly associated with post-menopausal osteoporosis.

[0005] The most vulnerable tissue in the bone to the effects of post-menopausal osteoporosis is the trabecular bone. This tissue is often referred to as spongy or cancellous bone and is particularly concentrated near the ends of the bone (near the joints) and in the vertebrae of the spine. The trabecular tissue is characterized by small osteoid structures which interconnect with each other, as well as the more solid and dense cortical tissue which makes up the outer surface and central shaft of the bone. This inter-connected network of trabeculae gives lateral support to the outer cortical structure and is critical to the biomechanical strength of the overall structure. In post-menopausal osteoporosis, it is, primarily, the net resorption and loss of the trabeculae which leads to the failure and fracture of bone. In light of the loss of the trabeculae in post-menopausal women, it is not surprising that the most common fractures are those associated with bones which are highly dependent on trabecular support, e.g., the vertebrae, the neck of the weight bearing bones such as the femur and the fore-arm. Indeed, hip fracture, collies fractures, and vertebral crush fractures are hall-marks of post-menopausal osteoporosis.

[0006] At this time, the only generally accepted method for treatment of post-menopausal osteoporosis is estrogen replacement therapy. Although therapy is generally successful, patient compliance with the therapy is low primarily because estrogen treatment frequently produces undesirable side effects.

[0007] Throughout premenopausal time, most women have less incidence of cardiovascular disease than age-matched men. Following menopause, however, the rate of cardiovascular disease in women slowly increases to match the rate seen in men. This loss of protection has been linked to the loss of estrogen and, in particular, to the loss of estrogen's ability to regulate the levels of serum lipids. The nature of estrogen's ability to regulate serum lipids is not well understood, but evidence to date indicates that estrogen can upregulate the low density lipid (LDL) receptors in the liver to remove excess cholesterol. Additionally, estrogen appears to have some effect on the biosynthesis of cholesterol, and other beneficial effects on cardiovascular health.

[0008] It has been reported in the literature that post-menopausal women having estrogen replacement therapy have a return of serum lipid levels to concentrations to those of the pre-menopausal state. Thus, estrogen would appear to be a reasonable treatment for this condition. However, the side-effects of estrogen replacement therapy are not acceptable to many women, thus limiting the use of this therapy. An ideal therapy for this condition would be an agent which would regulate the serum lipid level as does estrogen, but would be devoid of the side-effects and risks associated with estrogen therapy.

[0009] The third major pathology associated with post-menopausal syndrome is estrogen-dependent breast cancer and, to a lesser extent, estrogen-dependent cancers of other organs, particularly the uterus. Although such neoplasms are not solely limited to a post-menopausal women, they are more prevalent in the older, post-menopausal population. Current chemotherapy of these cancers has relied heavily on the use of anti-estrogen compounds such as, for example, tamoxifen. Although such mixed agonist-antagonists have beneficial effects in the treatment of these cancers, and the estrogenic side-effects are tolerable in acute life-threatening situations, they are not ideal. For example, these agents

may have stimulatory effects on certain cancer cell populations in the uterus due to their estrogenic (agonist) properties and they may, therefore, be contraproductive in some cases. A better therapy for the treatment of these cancers would be an agent which is an anti-estrogen compound having negligible or no estrogen agonist properties on reproductive tissues.

[0010]   In response to the clear need for new pharmaceutical agents which are capable of alleviating the symptoms of, *inter alia,* post-menopausal syndrome, the present invention provides new benzothiophene compounds, pharmaceutical compositions thereof, and methods of using such compounds for the treatment of post-menopausal syndrome and other estrogen-related pathological conditions such as those mentioned below.

[0011]   Uterine fibrosis (uterine fibroid disease) is an old and ever present clinical problem which goes under a variety of names, including uterine fibroid disease, uterine hypertrophy, uterine lieomyomata, myometrial hypertrophy, fibrosis uteri, and fibrotic metritis. Essentially, uterine fibrosis is a condition where there is an inappropriate deposition of fibroid tissue on the wall of the uterus.

[0012]   This condition is a cause of dysmenorrhea and infertility in women. The exact cause of this condition is poorly understood but evidence suggests that it is an inappropriate response of fibroid tissue to estrogen. Such a condition has been produced in rabbits by daily administrations of estrogen for 3 months. In guinea pigs, the condition has been produced by daily administration of estrogen for four months. Further, in rats, estrogen causes similar hypertrophy.

[0013]   The most common treatment of uterine fibrosis involves surgical procedures both costly and sometimes a source of complications such as the formation of abdominal adhesions and infections. In some patients, initial surgery is only a temporary treatment and the fibroids regrow. In those cases a hysterectomy is performed which effectively ends the fibroids but also the reproductive life of the patient. Also, gonadotropin releasing hormone antagonists may be administered, yet their use is tempered by the fact they can lead to osteoporosis. Thus, there exists a need for new methods for treating uterine fibrosis, and the methods of the present invention satisfy that need.

[0014]   Endometriosis is a condition of severe dysmenorrhea, which is accompanied by severe pain, bleeding into the endometrial masses or peritoneal cavity and often leads to infertility. The cause of the symptoms of this condition appear to be ectopic endometrial growths which respond inappropriately to normal hormonal control and are located in inappropriate tissues. Because of the inappropriate locations for endometrial growth, the tissue seems to initiate local inflammatory-like responses causing macrophage infiltration and a cascade of events leading to initiation of the painful response. The exact etiology of this disease is not well understood and its treatment by hormonal therapy is diverse, poorly defined, and marked by numerous unwanted and perhaps dangerous side effects.

[0015]   One of the treatments for this disease is the use of low dose estrogen to suppress endometrial growth through a negative feedback effect on central gonadotropin release and subsequent ovarian production of estrogen; however, it is sometimes necessary to use continuous estrogen to control the symptoms. This use of estrogen can often lead to undesirable side effects and even the risk of endometrial cancer.

[0016]   Another treatment consists of continuous administration of progestins which induces amenorrhea and by suppressing ovarian estrogen production can cause regressions of the endometrial growths. The use of chronic progestin therapy is often accompanied by the unpleasant CNS side effects of progestins and often leads to infertility due to suppression of ovarian function.

[0017]   A third treatment consists of the administration of weak androgens, which are effective in controlling the endometriosis; however, they induce severe masculinizing effects. Several of these treatments for endometriosis have also been implicated in causing a mild degree of bone loss with continued therapy. Therefore, new methods of treating endometriosis are desirable.

[0018]   The present invention relates to compounds of formula I
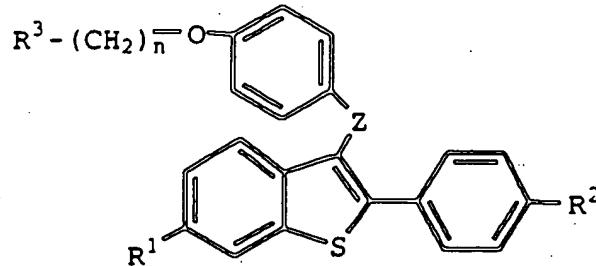
$$R^3 - (CH_2)_n - O - \text{(benzene ring)}$$

$$\begin{array}{c} Z \\ R^1 - \text{(benzothiophene)} - S - \text{(benzene ring)} - R^2 \end{array}$$

I

wherein

R^1 is -H, -OH, -O(C_1-C_4 alkyl), -OCOC$_6$H$_5$, -OCO(C_1-C_6 alkyl), or -OSO$_2$(C_2-C_6 alkyl);

R^2 is -H, -OH, -O(C_1-C_4 alkyl), -OCOC$_6$H$_5$, -OCO(C_1-C_6 alkyl), -OSO$_2$(C_2-C_6 alkyl) or halo;

R^3 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, di-ethylamino, diisopropylamino, or 1-hexamethyleneimino;

n is 2 or 3; and

z is -O- or -S-;

or a pharmaceutically acceptable salt thereof.

[0019] Further provided by the present invention are the following intermediate compounds which are useful for preparing pharmaceutically active compounds of the present invention, some of which are also pharmaceutically active:

II
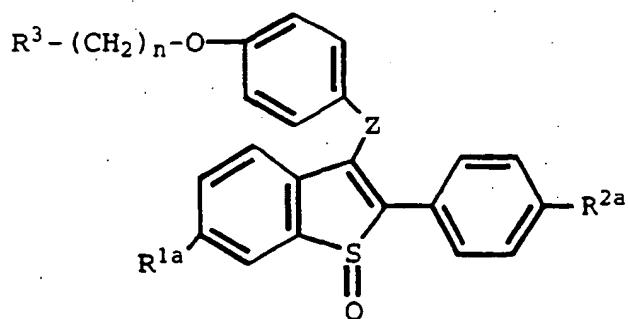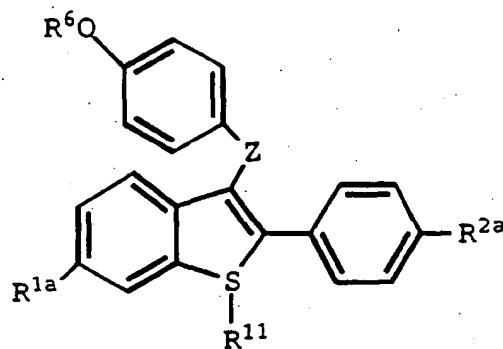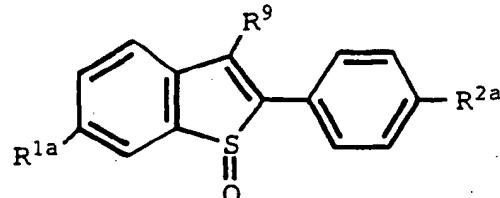
wherein

R^{1a} is -H or -OR^7 in which R^7 is a hydroxy protecting group;

R^{2a} is -H, halo, or -OR^8 in which R^8 is a hydroxy protecting group;

R^3 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, di-isopropylamino, or 1-hexamethyleneimino;

R^6 is -H or a hydroxy protecting group which can be selectively removed;

R^9 is a leaving group;
R^{11} is non-existent or $= O$;
n is 2 or 3; and
Z is -O- or -S-;

or a pharmaceutically acceptable salt thereof.

[0020]   Also provided is a process for preparing compounds of the formula

$$R^3-(CH_2)_n-O \cdots$$

wherein

R^{1a} is -H or $-OR^{7a}$ in which R^{7a} is -H or a hydroxy protecting group;
R^{2a} is -H, halo, or $-OR^{8a}$ in which R^{8a} is -H or a hydroxy protecting group;
R^3 is 1-piperidinyl, 1-pyrrolidino, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidino, 4-morpholino, dimethylamino, di-ethylamino, diisopropylamino, or 1-hexamethyleneimino;
n is 2 or 3; and
Z is -O- or -S-;

or a pharmaceutically acceptable salt thereof, comprising

a) oxidizing the sulfur atom of a formula IV compound

IV

wherein

R^{1a} and R^{2a} are as previously defined; and
R^9 is a leaving group;

b) reacting the product of step a), a compound of formula XIV

$$R^9$$

XIV

with a nucleophilic group of the formula

$$R^{12} \quad O-(CH_2)_n-R^3$$

wherein R^{12} is -OH or -SH;
c) reducing the product of step b), a compound of formula XVI

$$R^3-(CH_2)_n-O$$

XVI

to provide a compound of the formula

$$R^3-(CH_2)_n-O$$

;

d) optionally removing the R^{1a} and/or R^{2a} hydroxy protecting groups, when present, of the product of step c); and
e) optionally forming a salt of the product of step c) or step d).

[0021] The present invention further relates to pharmaceutical compositions containing compounds of formula I, optionally containing estrogen or progestin, and the use of such compounds, alone, or in combination with estrogen

or progestin, for alleviating the symptoms of post-menopausal syndrome, particularly osteoporosis, cardiovascular related pathological conditions, and estrogen-dependent cancer. As used herein, the term "estrogen" includes steroidal compounds having estrogenic activity such as, for example, 17b-estradiol, estrone, conjugated estrogen (Premarin®), equine estrogen 17b-ethynyl estradiol, and the like. As used herein, the term "progestin" includes compounds having progestational activity such as, for example, progesterone, norethylnodrel, nongestrel, megestrol acetate, norethindrone, and the like.

[0022]   The compounds of the present invention also are useful for inhibiting uterine fibroid disease and endometriosis in women, and aortal smooth muscle cell proliferation, particularly restenosis, in humans.

[0023]   One aspect of the present invention includes compounds of formula I
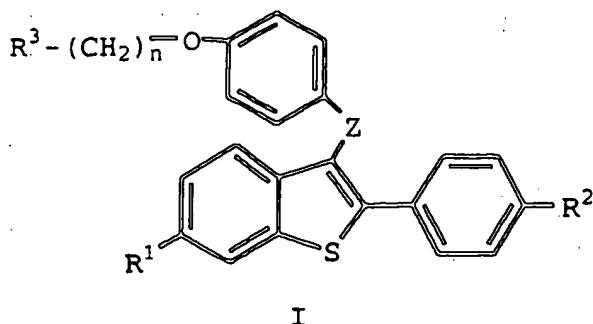
I

wherein

R^1 is -H, -OH, -O(C_1-C_4 alkyl), -OCOC$_6$H$_5$, -OCO(C_1-C_6 alkyl), or -OSO$_2$(C_2-C_6 alkyl);

R^2 is -H, -OH, -O(C_1-C_4 alkyl), -OCOC$_6$H$_5$, -OCO(C_1-C_6 alkyl), -OSO$_2$(C_2-C_6 alkyl), or halo;

R^3 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, diisopropylamino, or 1-hexamethyleneimino;

n is 2 or 3; and

z is -O- or -S-;

or a pharmaceutically acceptable salt thereof.

[0024]   General terms used in the description of compounds herein described bear their usual meanings. For example, "C_1-C_6 alkyl" refers to straight or branched aliphatic chains of 1 to 6 carbon atoms including moieties such as methyl, ethyl, propyl, isopropyl, butyl, n-butyl, pentyl, isopentyl, hexyl, isohexyl, and the like. Similarly, the term "C_1-C_4 alkoxy" represents a C_1-C_4 alkyl group attached through an oxygen molecule and include moieties such as, for example, methoxy, ethoxy, n-propoxy, isopropoxy, and the like.

[0025]   The starting material for one route for preparing compounds of formula I of the present invention, compounds of formula III, are prepared essentially as described by C. D. Jones in U.S. Pats. No. 4,418,068, and 4,133,814, each of which is herein incorporated by reference. Formula III has the structure

III
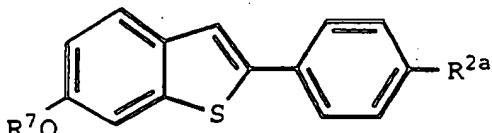
wherein R^7 and R^{2a} are as defined above.

[0026]   The R^7 and R^8 hydroxy protecting groups are moieties which generally are not found in the final, therapeutically active compounds of formula I, but which are intentionally introduced during a portion of the synthetic process to protect a group which otherwise might react in the course of chemical manipulations, and is then removed at a later stage of the synthesis. Since compounds bearing such protecting groups are of importance primarily as chemical intermediates (although some derivatives also exhibit biological activity), their precise structure is not critical. Numerous reactions for the formation, removal, and possibly, reformation of such protecting groups are described in a number of standard

works including, for example, *Protective Groups in Organic Chemistry*, Plenum Press (London and New York, 1973); Green, T.W., *Protective Groups in Organic Synthesis*, Wiley (New York, 1981); and *The Peptides*, Vol. I, Schrooder and Lubke, Academic Press, (London and New York, 1965).

[0027] Representative hydroxy protecting groups include, for example, $-C_1-C_4$ alkyl, $-C_1-C_4$ alkoxy, $-CO-(C_1-C_6$ alkyl), $-SO_2-(C_4-C_6$ alkyl), and -CO-Ar in which Ar is benzyl or optionally substituted phenyl. The term "substituted phenyl" refers to a phenyl group having one or more substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, nitro, halo, and tri(chloro or fluoro) methyl. The term "halo" refers to bromo, chloro, fluoro, and iodo.

[0028] For compounds of formula III, preferred R^7 and R^8 (R^{2a}) substituents are methyl, isopropyl, benzyl, and methoxymethyl. Compounds in which R^7 and R^8 each are methyl are prepared via the procedure described in the above-referenced Jones patent. Another preferred hydroxy protecting group is methoxymethyl. However, a formula IV compound, as shown below, is first prepared bearing the preferred methyl or other hydroxy protecting group(s). These protecting groups are then removed, forming phenolic moieties, which are then reprotected with methoxymethyl protecting groups.

[0029] Compounds of formula III are also prepared in which R^7 hydroxy protecting groups are selectively removed, leaving the R^8(R^{2a}) hydroxy protecting group as part of the final product. The same is true in which the R^8(R^{2a}) hydroxy protecting group is selectively removed, leaving the R^7 hydroxy protecting group in place. For example, R^7 is isopropyl or benzyl and R^8(R^{2a}) is methyl. The isopropyl or benzyl moiety is selectively removed via standard procedures, and the R^8 methyl protecting group is left as part of the final product.

[0030] The first steps of the present process for preparing certain compounds of formula I include selectively placing a leaving group at the 3 position of a formula III compound, coupling the reaction product of the first step with a 4-(protected-hydroxy)phenol, and removing the phenol's hydroxy protecting group. The present process is depicted in Scheme I below.

<u>Scheme I</u>

III

wherein R^7 and R^{2a} are as defined above

IV
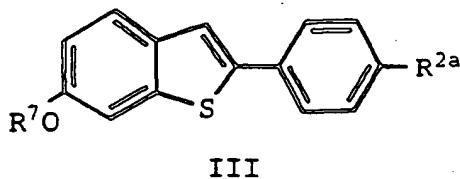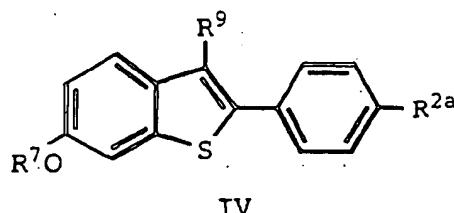
wherein R^9 is a leaving group

5

IIa

10
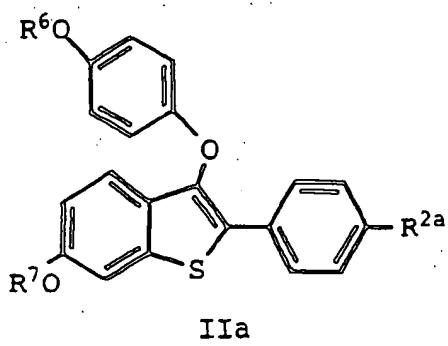
wherein R^6 is a hydroxy protecting group which can be selectively removed

20

25

IIb

30
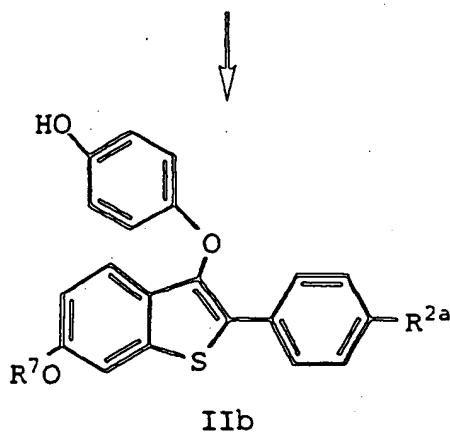
35 **[0031]** In the first step of Scheme I, an appropriate leaving group is selectively placed at the 3-position of the formula III starting material via standard procedures. Appropriate R^9 leaving groups include the sulfonates such as methanesulfonate, 4-bromobenzenesulfonate, toluenesulfonate, ethanesulfonate, isopropanesulfonate, 4-methoxybenzenesulfonate, 4-nitrobenzenesulfonate, 2-chlorobenzenesulfonate, triflate, and the like, halogens such as bromo, chloro, and iodo, and other related leaving groups. However, to insure proper placement of the leaving group, the named halogens
40 are preferred, and bromo is especially preferred.

[0032] The present reaction is carried out using standard procedures. For example, when the preferred halogenating agents are used, an equivalent of such a halogenating agent, preferably bromine, is reacted with an equivalent of the formula III substrate, in the presence of a suitable solvent such as, for example, chloroform or acetic acid. The reaction is run at a temperature from about 40° C to about 80° C.

45 **[0033]** The reaction product from the above process step, a compound of formula IV, is then reacted with a 4-(protected-hydroxy)phenol to form compounds of formula IIa in which R^6 is a selectively removable hydroxy protecting group. Generally, the 4-hydroxy protecting moiety of the phenol may be any known protecting group which can be selectively removed without removing, in this instance, the R^7 and, when present, R^8 moieties of a formula IIa compound. Preferred R^6 protecting groups include methoxymethyl, when R^7 and/or R^8 are not methoxymethyl, and benzyl.
50 Of these, benzyl is especially preferred. The 4-(protected-hydroxy)phenol reactants are commercially available or can be prepared via standard procedures.

[0034] This coupling reaction is known in the art as an Ullman reaction and is run according to standard procedures [see, e.g., *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* Fourth Edition, 3-16, (J. March, ed., John Wiley & Sons, Inc. 1992); Jones, C.D., *J. Chem. Soc. Perk. Trans. I,* 4:407 (1992)].

55 **[0035]** In general, equivalent amounts of the two aryl substrates, in the presence of up to an equimolar amount of a copper(I) oxide catalyst and an appropriate solvent, are heated to reflux under an inert atmosphere. Preferably, an equivalent of a formula IV compound in which R^9 is bromo is reacted with an equivalent amount of 4-benzyloxyphenol in the presence of an equivalent of cuprous oxide.

VI

Ia

wherein R^3, R^7, R^{2a}, and n are as defined above, and R^{2b} is -H, -OH, or halo.

[0046] In the first step of the process shown in Scheme II, the alkylation is carried out via standard procedures. Compounds of formula V are commercially available or are prepared by means well known to one of ordinary skill in the art. Preferably, the hydrochloride salt of a formula V compound, particularly 2-chloroethylpiperidine hydrochloride, is used.

[0047] Generally, at least about 1 equivalent of formula IIb substrate are reacted with 2 equivalents of a formula V compound in the presence of at least about 4 equivalents of an alkali metal carbonate, preferably cesium carbonate, and an appropriate solvent.

[0048] Solvents for this reaction are those solvents or mixture of solvents which remain inert throughout the reaction. N,N-dimethylformamide, especially the anhydrous form thereof, is preferred.

[0049] The temperature employed in this step should be sufficient to effect completion of this alkylation reaction. Typically, ambient temperature is sufficient and preferred.

[0050] The present reaction preferably is run under an inert atmosphere, particularly nitrogen.

[0051] Under the preferred reaction conditions, this reaction will run to completion in about 16 to about 20 hours. Of course, the progress of the reaction can be monitored via standard chromatographic techniques.

[0052] As an alternative for preparing compounds of formula VI, a formula IIb compound is reacted with an excess of an alkylating agent of the formula

$$Q - (CH_2)_n - Q'$$
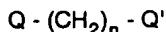
wherein Q and Q' each are the same or different leaving group, in an alkali solution. Appropriate leaving groups are the aforementioned leaving groups used in the preparation of compounds of formula IV.

[0053] A preferred alkali solution for this alkylation reaction contains potassium carbonate in an inert solvent such as, for example, methyethyl ketone (MEK) or DMF. In this solution, the 4-hydroxy group of the benzoyl moiety of a formula IIb compound exists as a phenoxide ion which displaces one of the leaving groups of the alkylating agent.

[0054] This reaction is best when the alkali solution containing the reactants and reagents is brought to reflux and allowed to run to completion. When using MEK as the preferred solvent, reaction times run from about 6 hours to about 20 hours.

[0055] The reaction product from this step is then reacted with 1-piperidine, 1-pyrrolidine, methyl-1-pyrrolidine, dimethyl-1-pyrrolidine, 4-morpholine, dimethylamine, diethylamine, diisopropylamine, or 1-hexamethyleneimine, via standard techniques, to form compounds of formula VI. Preferably, the hydrochloride salt of piperidine is reacted with the alkylated compound of formula IIb in an inert solvent, such as anhydrous DMF, and heated to a temperature in the range from about 60° C to about 110° C. When the mixture is heated to a preferred temperature of about 90° C, the reaction only takes about 30 minutes to about 1 hour. However, changes in the reaction conditions will influence the amount of time this reaction needs to be run for completion. Of course, the progress of this reaction step can be monitored via standard chromatographic techniques.

[0056] Compounds of formula VI, in which R^7 and when present, R^8 each are C_1-C_4 alkyl, preferably methyl, and in which R^{2a} is -H or halo, are novel and are pharmaceutically active for the methods herein described. Accordingly, such compounds are encompassed by the definition herein of compounds of formula I.

[0057] Certain preferred compounds of formula I are obtained by cleaving the R^7 and, when present, R^8 hydroxy protecting groups of formula VI compounds via well known procedures. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, *Protective Groups in Organic Chemistry,* Plenum Press (London and New York, 1973); Green, T.W., *Protective Groups in Organic Synthesis,* Wiley, (New York, 1981); and *The Peptides,* Vol. I, Schrooder and Lubke, Academic Press (London and New York, 1965). Methods for removing preferred R^7 and/or R^8 hydroxy protecting groups, particularly methyl and methoxymethyl, are essentially as described in the Examples, *infra.*

[0058] Compounds of formula Ia are novel, are pharmaceutically active for the methods herein described, and are encompassed by formula I as defined herein.

[0059] Compounds of formula I in which R^1 is -H are prepared via the synthetic route shown below in Scheme III. Using this route, a 3-position leaving group (R^9) is placed on commercially available thianaphthene (formula VII) to form a compound of formula VIII, which is then coupled with a 4-(protected-hydroxy)phenol, providing compounds of formula IX.

Scheme III

VII

VIII

IX
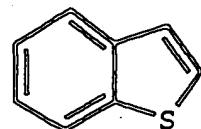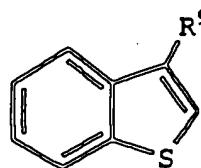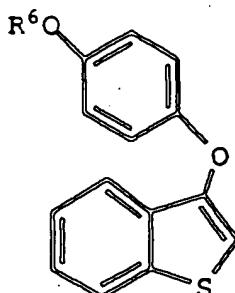
wherein R^6 is a hydroxy protecting group which can be selectively removed and R^9 is a leaving group.

[0060] The compound of formula VII is commercially available. Preparation of formulae VIII and IX compounds, including the definition of R^6 and R^9 substituents, as well as preferred reactants and conditions, unless otherwise herein stated, are the same as described above and shown in Scheme I, *supra*.

[0061] Compounds of formula IX are then arylated via Suzuki coupling [see, e.g., Suzuki, A., *Pure and Appl. Chem.*, 6(2):213-222 (1994)]. Using one Suzuki coupling option, a formula IX compound is selectively halogenated at the 2-position, and then coupled with an arylboronic acid compound of formula XIa (Route A of Scheme IV below).

[0062] Preferably, however, an arylboronic acid of formula Xb is formed from a compound of formula IX, and then reacted with a halo-arene of formula XIb to give novel intermediates of formula IIc (Route B of Scheme IV below). Such novel intermediates are useful for preparing pharmaceutically active compounds of the present invention (formula Ib compounds) via alkylation and deprotection.

Scheme IV

IX

Route A

Xa

Route B

Xb

XIa

XIb

IIc

IIc

5

10

HO

O

15

IId

R^{2a}

20

25

$R^3 - (CH_2)_n - O$

O

30

XII

R^{2a}

35

S

40

45

$R^3 - (CH_2)_n - O$

O

50

Ib

R^{2b}

S
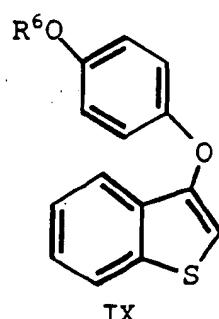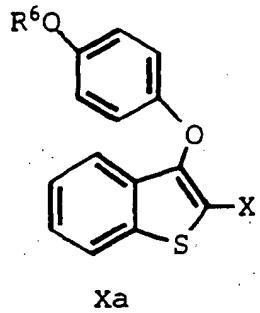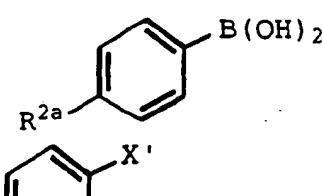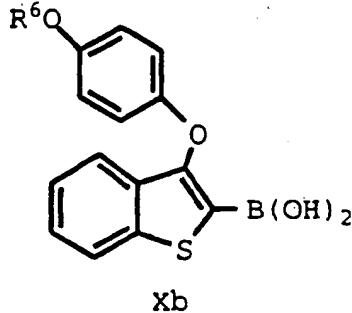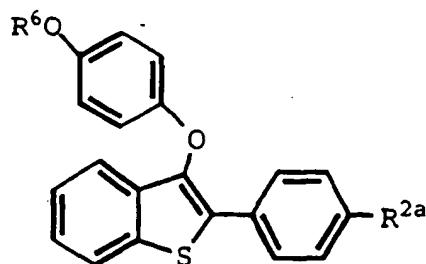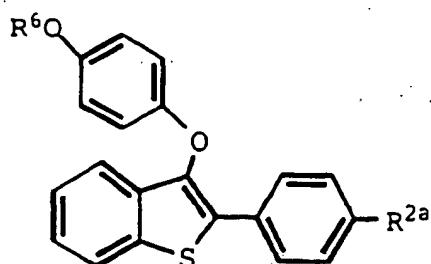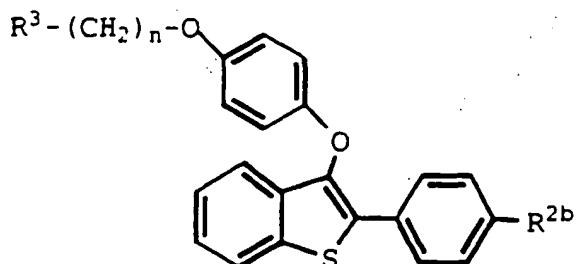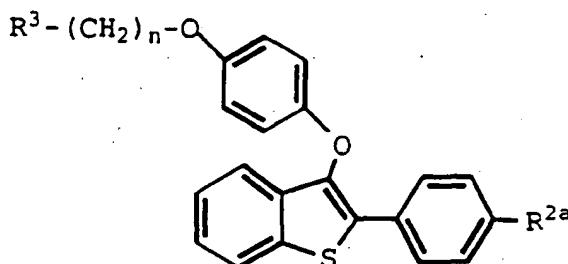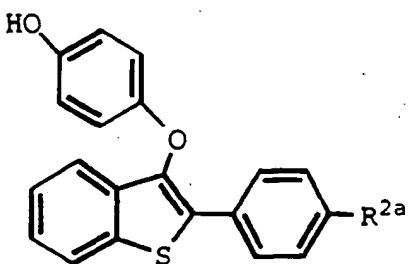
wherein

R^{2a}, R^{2b}, R^3, R^6 and n are as defined above;
X is iodo, bromo, or fluoro, in the order of preference; and

X' is iodo, bromo, or fluoro, in the order of preference, or triflate.

[0063] The first step in Route A in Scheme IV is the 2-position iodination or bromination of a formula IX compound using standard procedures. Generally, a formula IX compound is reacted with a slight excess of n-butyllithium in hexane, in an appropriate solvent and under an inert atmosphere such as nitrogen, followed by the dropwise addition of a slight excess of the desired halogenating agent in an appropriate solvent. Preferably, the halogenating agent for this step is iodine, but the use of bromine, N-bromosuccinimide is also permitted.

[0064] Appropriate solvents include an inert solvent or mixture of solvents such as, for example, diethyl ether, dioxane, and tetrahydrofuran (THF). Of these, tetrahydrofuran, particularly anhydrous THF, is preferred.

[0065] The present selective, 2-position halogenation reaction optionally is run at a temperature from about -75° C to about 85° C.

[0066] The product of the above reaction, a halo-arene of formula Xa, is then coupled with an arylboronic acid of formula XIa, via standard Suzuki coupling procedures, to provide compounds of formula IIc. Compounds of formula XIa, in which R^{2a} is -H, halo, or -OR^8 (R^8 is a hydroxy protecting group as defined, *supra*) are derived from commercially available compounds via procedures well known to one of ordinary skill in the art (see, e.g., March J.; and Suzuki, A., *supra*).

[0067] In the present coupling reaction, a slight excess of a formula XIa compound is reacted with each equivalent of a formula Xa compound in the presence of a palladium catalyst and an appropriate base in an inert solvent such as toluene.

[0068] Although various palladium catalysts drive Suzuki coupling reactions, the catalyst selected usually is reaction specific. Thus, the use of tetrakistriphenylphosphine palladium in the present reaction is highly preferred.

[0069] Likewise, various bases may be used in the present coupling reaction. However, it is preferred to use an alkali metal carbonate, particularly 2N sodium carbonate.

[0070] The temperature employed in this step should be sufficient to effect completion of the coupling reaction. Typically, heating the reaction mixture to reflux for a period from about 2 to about 4 hours is adequate and preferred.

[0071] In Route B of Scheme IV, a 2-position arylboronic of formula Xb is prepared using well known procedures. Generally, a compound of formula IX is treated with a slight excess of n-butyllithium in hexanes, in an appropriate solvent and under an inert atmosphere such as nitrogen, following by the dropwise addition of an appropriate trialkyl-borate.

[0072] Appropriate solvents include an inert solvent or mixture of solvents such as, for example, diethyl ether, dioxane, and tetrahydrofuran (THF). THF, particularly anhydrous THF, is preferred.

[0073] The preferred trialkylborate used in the present reaction is triisopropyl borate.

[0074] The product of this reaction, a compound of formula Xb, is then reacted with a aryl halide or aryl triflate of formula XIb, via standard Suzuki coupling procedures, to provide compounds of formula IIc. The preferred reaction conditions for the present reaction are as described for the reaction of compounds of formulae XIa and Xa, in Scheme IV, which also provide compounds of formula IIc.

[0075] The transformation of compounds of formula IIc to formula Ia compounds is carried out as described above for the conversion of formula IIa compounds to compounds of formula Ia.

[0076] Compounds of formulae IIc and IId are novel, and are useful for the preparation of pharmaceutically active compounds of the present invention.

[0077] Compounds of formulae XII and Ib also are novel, are useful for the methods herein described, and are encompassed by formula I as herein defined.

[0078] Compounds of formula I in which either R^1 or R^2 is -H and the other R^1 or R^2 substituent is -OH also are prepared from compounds of formula I in which both R^1 or R^2 are -OH. The dihydroxy compound of formula I is converted to a mixture of 6- and 4'- monotriflates, and the triflate moiety is reduced to hydrogen [see, Saa, J.M., et al., *J. Org. Chem.*, 55:991 (1990)]. The resulting mixture of monohydroxy derivatives, either as the free base or pharmaceutically acceptable salt, preferably the hydrochloride salt, can then be separated by standard crystallization techniques.

[0079] In general, a dihydroxy compound of formula I is treated with about 4 to about 6 equivalents of a amine base, such as triethylamine, in a non-reactive solvent followed by the addition of 1 equivalent of trifluoromethanesulfonic anhydride. A statistical mixture of mono- and di-triflates are produced and separated by standard chromatographic techniques. A preferred solvent for this step is anhydrous dichloromethane.

[0080] When run at a temperature range from about 0° C to about 25° C, the present reaction is completed within from about 1 to about 5 hours.

[0081] The isolated mixture of mono-triflated compounds is then hydrogenated, in a non-reactive solvent, in the presence of from about 3 to about 6 equivalents of an amine base, preferably triethylamine, and a hydrogenation catalyst such as palladium-on-carbon, which is preferred. Preferred solvents for this reaction include ethyl acetate and ethanol or, alternatively, a mixture thereof. When this step of the present reaction is run under about 40 psi of hydrogen gas, at ambient temperature, the reaction time is from about 2 hours to about 5 hours.

[0082] The resulting mixture of monohydroxy derivatives of formula I have different solubilities in ethyl aceate and the 6-hydroxy-4'-hydrogen derivatives can be partially separated from the 6-hydrogen-4'-hydroxy derivatives by selective crystallization. Further separation, which provides pure monohydroxy compounds of formula I, can be achieved by conversion of the enriched mixtures to the hydrochloride salts followed by crystallization from ethyl acetate-ethanol.

[0083] A more direct method for the preparation of compounds of formula I in which either R^1 or R^2 is -H and the other R^1 or R^2 substituent is -OH, as well as an alternative method for the preparation of compounds of formula I in which either R^1 or R^2 is -H and the other R^1 or R^2 substituent is -O-(C_1-C_4 alkyl) uses a compound of the formula

$$R^3-(CH_2)_n-O$$
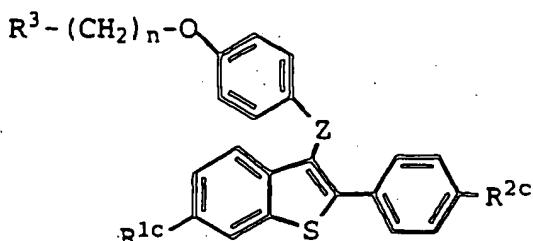
wherein

R^3 and n are defined above;
R^{1c} is -OH or -O-(C_1-C_4 alkyl); and
R^{2c} is -OH or -O-(C_1-C_4 alkyl);

providing when R^{1c} is -OH, R^{2c} is -O-(C_1-C_4 alkyl), and when R^{1c} is -O-(C_1-C_4 alkyl) R^{2c} is -OH.

[0084] In this process, the hydroxy moiety of such a compound is converted to a triflate derivative by treatment with trifluoromethane sulfonic anhydride. The triflate moiety is then reduced under standard conditions, preferably by catalytic hydrogenation. The hydroxy protecting moiety is then removed via standard procedures, as in those herein described, providing compounds of formula I in which either R^1 or R^2 is -H and the other R^1 or R^2 substituent is -OH.

[0085] Another alternative, and preferred, method for the preparation of compounds of the present invention is shown in Scheme V. In the present process, the sulfur atom of a formula IV compound (infra) is oxidized to form a sulfoxide (formula XIV), which is then reacted with a nucleophilic group to introduce the oxygen or sulphur atom linker of formula I and formula II compounds. The sulfoxide moiety of formula XVI compounds is then reduced to provide certain compounds of the present invention.

Scheme V
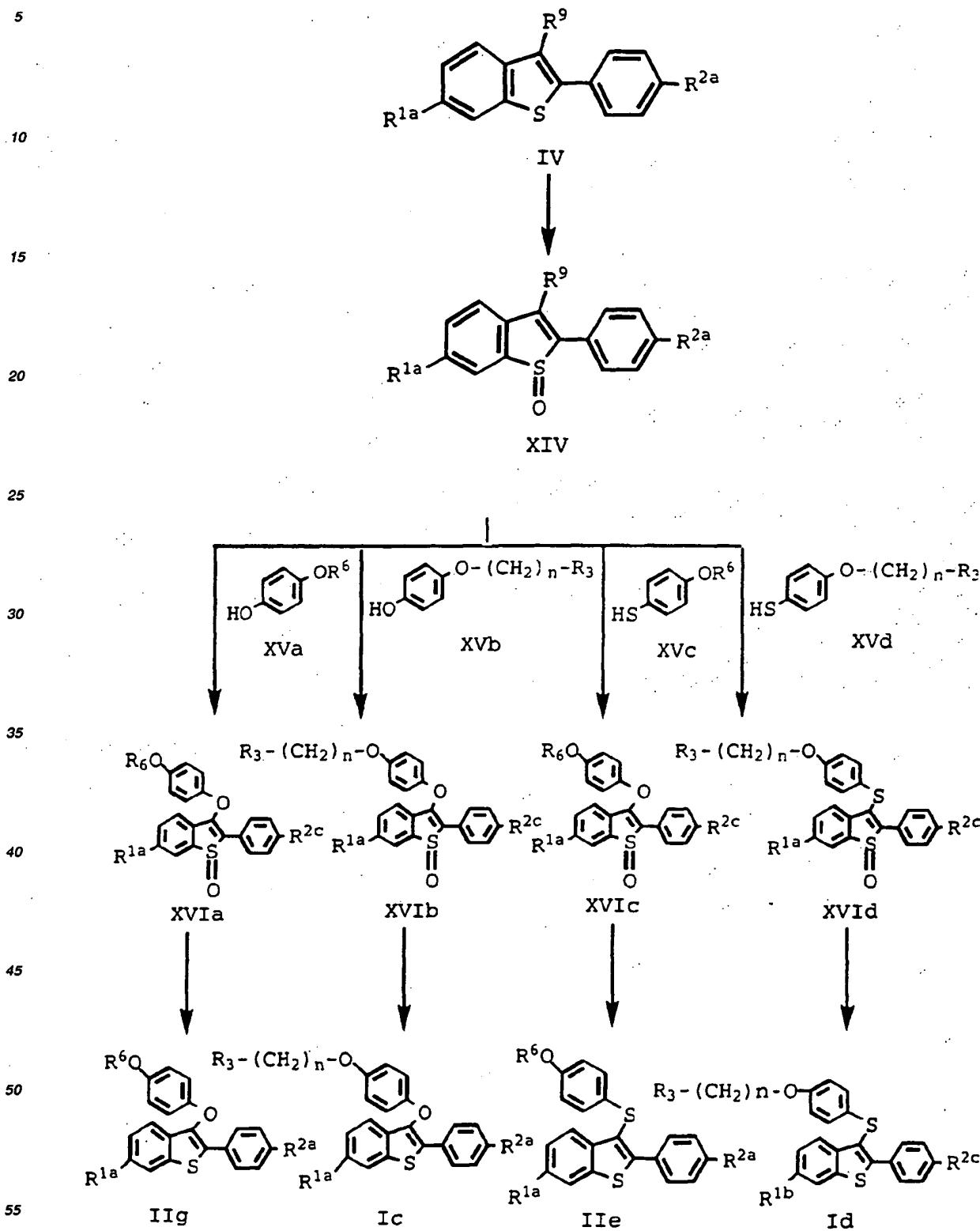
wherein each variable has its previously defined meaning.

[0086] In the first step of this process, a compound of formula IV is selectively oxidized to the sulfoxide. A number of known methods are available for the process step [see, e.g., Madesclaire, M., Tetrahedron, 42 (20); 5459-5495 (1986); Trost, B.M., et al., Tetrahedron Letters, 22 (14); 1287-1290 (1981); Drabowicz, J., et al., Synthetic Communications, 11 (12); 1025-1030 (1981); Kramer, J.B., et al., 34th National Organic Symposium, Williamsburg, VA., June 11-15, 1995]. However, many oxidants provide only poor conversion to the desired product as well as significant over-oxidation to the sulfone. The present, novel process, however, converts a formula IV compound to a sulfoxide of formula XIV in high yield with little or no formation of sulfones. This process involves the reaction of a formula IV compound with about 1 to about 1.5 equivalents of hydrogen peroxide in a mixture of about 20% to about 50% trifluoroacetic acid in methylene chloride. The reaction is run at a temperature from about 10° C to about 50° C, and usually required from about 1 to about 2 hours to run to completion.

[0087] Next, the 3-position leaving group (R^9) is displaced by the desired nucleophilic derivative of formula XV. Such nucleophilic derivatives are prepared via standard methods.

[0088] In this step of the process, the acidic proton of the nucleophilic group is removed by treatment with a base, preferably a slight excess of sodium hydride or potassium tertbutoxide, in a polar aprotic solvent, preferably DMF or tetrahydrofuran. Other bases that can be employed include potassium carbonate and cesium carbonate. Additionally, other solvents such as dioxane or dimethylsulfoxide can be employed. The deprotonation is usually run at a temperature between about 0° C and about 30° C, and usually requires about 30 minutes for completion. A compound of formula XIV is then added to the solution of the nucleophile. The displacement reaction is run at a temperature between 0° C and about 50° C, and is usually run in about 1 to about 2 hours. The product is isolated by standard procedures.

[0089] When a benzyl moiety is used as a hydroxy protecting group, hydrogenolysis of the sulfoxide moiety will also provide removal of the benzyl protecting group, eliminating the requirement for selectively removing such a group at a later stage in the process.

[0090] In the next step of the present process, novel sulfoxides of formulae XVI a, b, c, and d (collectively formula XVI) are reduced to a benzothiophene compound of formulae IIg, Ic, IIe, and Id, respectively. Prior to the present reduction process, compounds of formulae IIg and IIe can first be alkylated as herein described. Reduction of the sulfoxide compounds can be accomplished by using one of a multitude of methods known in the art including, for example, hydride reduction (lithium aluminum hydride), catalytic hydrogenation, transfer hydrogenolysis and trimethylsilyl iodide (TMS-I). In this reduction, the choice of reagent is dependent upon the compatibility of other functionalities in the molecule. For the compounds described in the present invention, lithium aluminum hydride ($LiAlH_4$) and transfer hydrogenolysis (palladium black/ammonium formate) are the preferred reagents. For $LiAlH_4$ reduction, appropriate solvents such as, for example, diethyl ether, dioxane, and tetrahydrofuran (THF). Of these, THF, particularly anhydrous THF, is preferred. For transfer hydrogenolysis, alcohol solvents, particularly ethanol, is preferred. The reaction is run at a temperature from about 0° C to about 60° C, and requires from about 0.5 hours to about 2 hours for completion.

[0091] When desired, the hydroxy protecting group or groups of the products of the process shown in Scheme V can be removed, and a salt of the product of any step of the process. Accordingly, the present invention provides a process for preparing compounds of the formula

wherein

R^{1a} is -H or -OR^{7a} in which R^{7a} is -H or a hydroxy protecting group;
R^{2a} is -H, halo, or -OR^{8a} in which R^{8a} is -H or a hydroxy protecting group;
R^3 is 1-piperidinyl, 1-pyrrolidino, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidino, 4-morpholino, dimethylamino, diethylamino, diisopropylamino, or 1-hexamethyleneimino;
n is 2 or 3; and
Z is -O- or -S-;

or a pharmaceutically acceptable salt thereof, comprising

a) oxidizing the sulfur atom of a formula IV compound

IV

wherein

R^{1a} and R^{2a} are as previously defined; and
R^9 is a leaving group;

b) reacting the product of step a), a compound of formula XIV

XIV

with a nucleophilic group of the formula

wherein R^{12} is -OH or -SH;
c) reducing the product of step b), a compound of formula XVI

21

$$R^3 - (CH_2)_n - O \text{—} \quad Z$$

XVI

to provide a compound of the formula

;

d) optionally removing the R^{1a} and/or R^{2a} hydroxy protecting groups, when present, of the product of step c); and
e) optionally forming a salt of the product of step c) or step d).

[0092]   This novel process also provides novel compounds of formulae XIV, and XVI a, b, c, and d, each of which is an intermediate useful for preparing the pharmaceutically active compounds of the present invention.

[0093]   Compounds of formulae I in which Z is S are also prepared using the process described below in Scheme VI in which a compound of formula IVa is metallated. The resulting product, a compound of formula XVII is reacted with a 4-(protected hydroxy)phenyl disulfide of formula XVIII, and the phenol protecting group of a formula IIe compound is removed to provide compounds of formula IIf. One will note that, in using this process, R^2 cannot be halo because of chemical limitations.

Scheme VI

5

IVa

10

15

XVII

20

25

XVIII

30

35

IIe

40

45

50

55

IIf
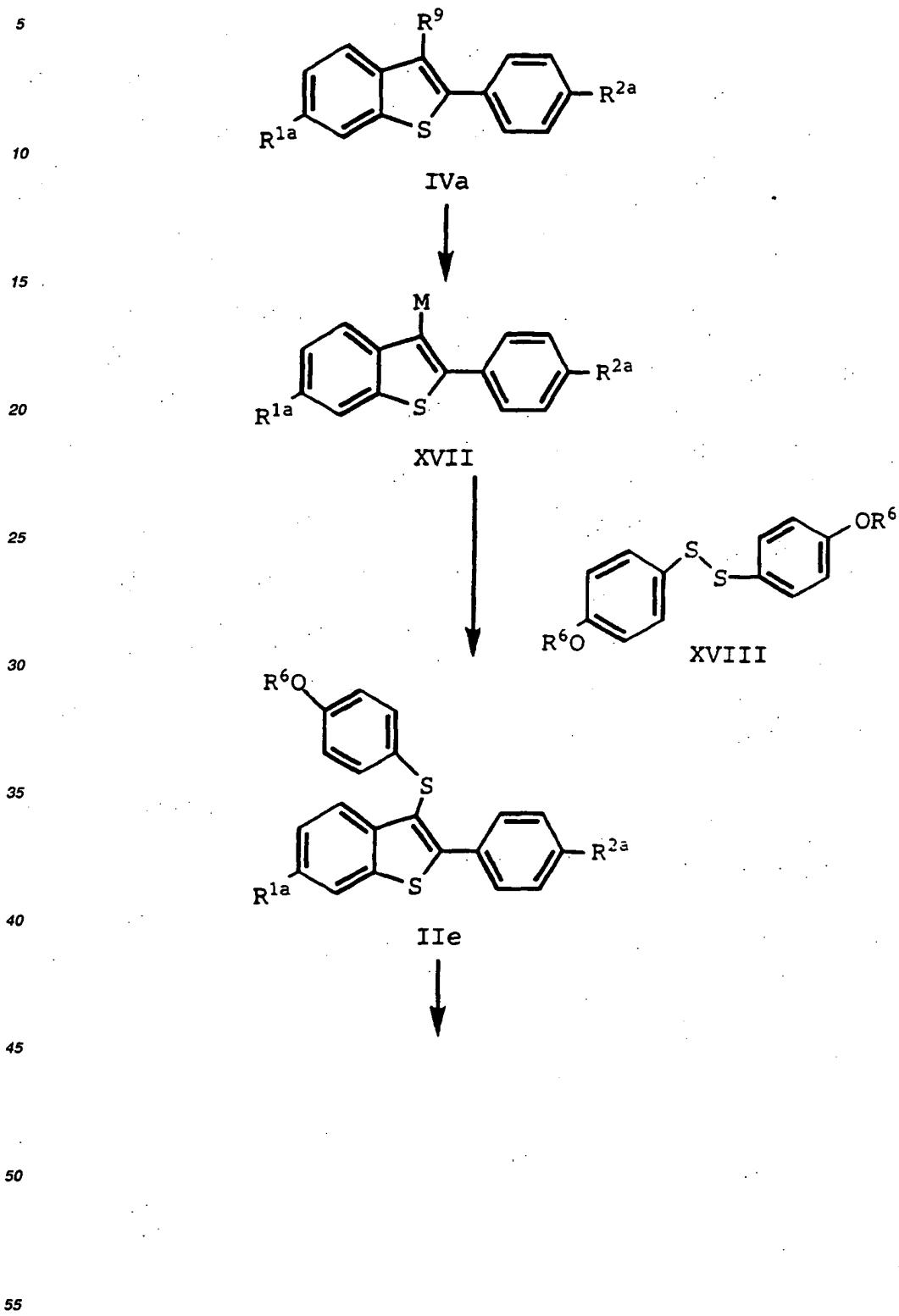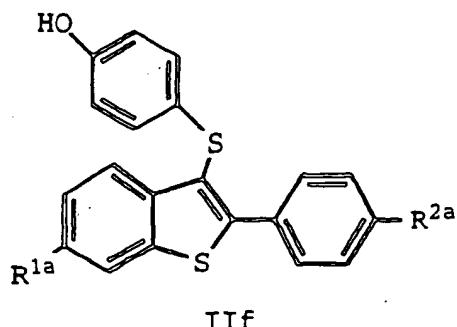
wherein

R^{1a} is -H or -OR^7 and R^7 is a hydroxy protecting group;

R^{2a} is -H, or -OR^8 and R^8 is a hydroxy protecting group;

R^6 is a hydroxy protecting group which can be selectively removed;

R^9 is a leaving group; and

M is a metal ion.

[0094] In the first two steps of Scheme VI, a formula IVa compound is metallated via well known procedures. Most commonly, and preferably, a formula IVa compound is treated with a slight excess of n-butyllithium in hexanes in an appropriate solvent, followed by the dropwise addition of a solution of a disulfide compound of formula XVIII in an appropriate solvent.

[0095] Both of these reaction steps are run under an inert atmosphere such as nitrogen, while appropriate solvents for both steps include one or more inert solvents such as diethyl ether, dioxane, and THF. Of these, THF, particularly the anhydrous form thereof, is preferred. In addition, the present reaction steps are run at a temperature from about -78° C to about 85° C.

[0096] In the first step of the present reaction, a metallated compound of formula XVII is provided. The 4-(protected-hydroxy)phenyl disulfide (a formula XVIII compound) which is reacted with such a formula XVII compound to give a compound of formula IIe, is prepared by protecting the hydroxy group of commercially available 4-hydroxyphenylsulfide with an appropriate protecting group via procedures known in the art. A preferred R^6 protecting group is methoxymethyl, providing R^7 and R^8, if either or both are present, is a hydroxy protecting group other than methoxymethyl. It is imperative that the R^6 hydroxy protecting group is a moiety different than those formed by R^7 and R^8 hydroxy protecting groups, when present, so that the R^6 group can selectively be removed, via standard procedures, to provide compounds of formula IIf.

[0097] To effect deprotection by removal of the R^6 protecting group, a formula IIe compound in a protic solvent or mixture of solvents is reacted in an acid media containing at least one equivalent of acid, preferably methanesulfonic acid, and heating from about 25° to about 110° C. Typically, the reaction time is from about 6 to about 24 hours, but the progress of the reaction may be monitored via standard chromatographic techniques.

[0098] Appropriate solvents for the present reaction include, for example, water and methanol.

[0099] Compounds of formulae IIe and IIf are novel, are useful for preparing pharmaceutically active compounds of formula I and are herein encompassed within the above depiction of formula II.

[0100] Compounds of formula Id

$$R_3-(CH_2)n-O-\bigcirc-S-\cdots$$

Id
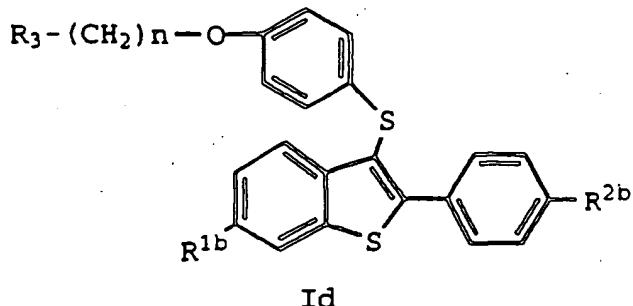
wherein

R^{1b} is -H or -OH;

R^{2b} is -H or -OH; and

R^3 and n, are as defined above, are prepared by using the above-described procedures related to the process steps shown in Schemes II and IV. Such compounds of formula Id also are novel, are useful for the methods of the present invention, and are herein encompassed within the above depiction of formula I.

[0101]   Compounds of formula I, in which R^1 and R^2 are different hydroxy protecting groups or either R^1 and R^2 is a hydroxy protecting group and the other is hydroxy are selectively prepared by using a modified 2-arylbenzothiophene starting material of formula III above, providing that hydroxy protecting groups designated R^7 and R^8 are sufficiently different so that one protecting group is removed while the other group remains. Such 2-arylbenzothiophenes are prepared via procedures well known in the art.

[0102]   Particularly useful for the preparation of formula I compounds in which R^1 and R^2 are different protecting groups is Suzuki coupling as described above in Scheme IV. However, 6-(protected hydroxy) benzothiophene-2-boronic acid is reacted with a formula XIb compound above in which R^{2a} is $-OR^8$ and R^7 does not equal R^8. This reaction allows preparation of compounds of the present invention in which R^7 and R^8 are different hydroxy protecting groups so that one protecting group may selectively be removed and the other remains as a moiety of the final product. Preferably, the R^7 protecting group, especially benzyl or isopropyl, is removed to form a hydroxy moiety while the R^8 protecting group, particularly methyl, remains.

[0103]   Suzuki coupling also is accomplished by using the above-described procedures but replacing a formula XIb compound with a compound of formula XIX

$$\bigcirc-R^{10}$$
$$R^{8a}$$

XIX
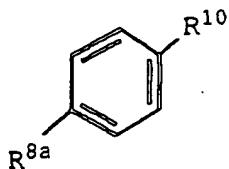
wherein

R^{8a} is C_1-C_6 alkyl sulfonate, preferably methansulfonate or C_4-C_6 aryl sulfonate; and

R^{10} is a leaving group, preferably bromo or triflate.

[0104]   In this process, a 6-(protecting hydroxy) benzothiophene-2-boronic acid as described above is reacted with a compound of formula XIX to provide a compound of formula XX, which is reacted with boron tribromide in methylene chloride to provide a monohydroxy compound which is subsequently converted to, for example, a benzyl moiety by standard procedures (formula XXI). The 4'-sulfonate ester is then selectively removed by basic hydrolysis or, preferably, by treatment with $LiAlH_4$, in an appropriate aprotic solvent such as, for example, THF. This reaction provides a compound of formula XXII which is finally, for example, methylated at the 4'-position via standard procedures (formula IIIa). Of course, one skilled in the art will recognize that various processes can be utilized to provide formula IIIa compounds

in which the hydroxy protecting groups are other than shown in Scheme VII below, but which can be selectively removed to provide monohydroxy compounds of formula I of the present invention.

Scheme VII

XX

XXI
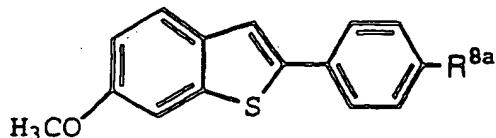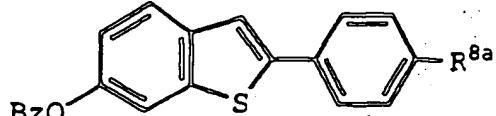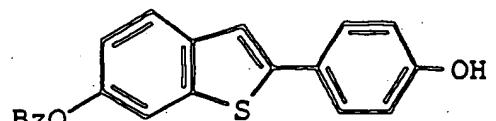
XXII
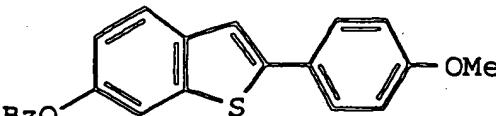
IIIa

Compounds of IIIa are then subjected to the various processes herein described to provide compounds of formula I and II of the present invention.

[0105]   Other preferred compounds of formula I are prepared by replacing 6- and/or 4'-position hydroxy moieties, when present, with a moiety of the formula -O-CO-(C_1-C_6 alkyl), or -O-SO_2-(C_2-C_6 alkyl) via well known procedures. See, e.g., U.S. Pat. No. 4,358,593.

[0106]   For example, when an -O-CO(C_1-C_6 alkyl) group is desired, a mono- or dihydroxy compound of formula I is reacted with an agent such as acyl chloride, bromide, cyanide, or azide, or with an appropriate anhydride or mixed anhydride. The reactions are conveniently carried out in a basic solvent such as pyridine, lutidine, quinoline or isoquinoline, or in a tertiary amine solvent such as triethylamine, tributylamine, methylpiperidine, and the like. The reaction also may be carried out in an inert solvent such as ethyl acetate, dimethylformamide, dimethylsulfoxide, dioxane, dimethoxyethane, acetonitrile, acetone, methyl ethyl ketone, and the like, to which at least one equivalent of an acid scavenger (except as noted below), such as a tertiary amine, has been added. If desired, acylation catalysts such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine may be used. See, e.g., Haslam, et al., Tetrahedron, 36:2409-2433 (1980).

[0107]   The present reactions are carried out at moderate temperatures, in the range from about -25° C to about 100° C, frequently under an inert atmosphere such as nitrogen gas. However, ambient temperature is usually adequate for the reaction to run.

[0108]   Acylation of a 6-position and/or 4'-position hydroxy group also may be performed by acid-catalyzed reactions of the appropriate carboxylic acids in inert organic solvents. Acid catalysts such as sulfuric acid, polyphosphoric acid, methanesulfonic acid, and the like are used.

[0109]   The aforementioned R^1 and/or R^2 groups of formula I compounds also may be provided by forming an active ester of the appropriate acid, such as the esters formed by such known reagents such as dicyclohexylcarbodiimide, acylimidazoles, nitrophenols, pentachlorophenol, N-hydroxysuccinimide, and 1-hydroxybenzotriazole. See, e.g., Bull. Chem. Soc. Japan, 38:1979 (1965), and Chem. Ber., 788 and 2024 (1970).

[0110]   Each of the above techniques which provide -O-CO-(C_1-C_6 alkyl) moieties are carried out in solvents as discussed above. Those techniques which do not produce an acid product in the course of the reaction, of course, do not call for the use of an acid scavenger in the reaction mixture.

[0111]   When a formula I compound is desired in which the 6- and/or 4'-position hydroxy group of a formula I compound is converted to a group of the formula -O-SO_2-(C_2-C_6 alkyl), the mono- or dihydroxy compound is reacted with, for example, a sulfonic anhydride or a derivative of the appropriate sulfonic acid such as a sulfonyl chloride, bromide, or sulfonyl ammonium salt, as taught by King and Monoir, J. Am. Chem. Soc., 97:2566-2567 (1975). The dihydroxy compound also can be reacted with the appropriate sulfonic anhydride or mixed sulfonic anhydrides. Such reactions are carried out under conditions such as were explained above in the discussion of reaction with acid halides and the like.

[0112]   Although the free-base form of formula I compounds can be used in the methods of the present invention, it is preferred to prepare and use a pharmaceutically acceptable salt form. Thus, the compounds used in the methods of this invention primarily form pharmaceutically acceptable acid addition salts with a wide variety of organic and inorganic acids, and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, b-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzenesulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. Preferred salts are the hydrochloride and oxalate salts.

[0113]   The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or ethyl acetate. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

[0114]   The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

[0115]   Representative preferred compounds of the present invention include the following:

Group I:

[6-methoxy-2-(4-methoxyphenyl)-3-bromo]benzo[b] thiophene-(S-oxide)

[6-isopropoxy-2-(4-methoxyphenyl)-3-bromo]benzo[b] thiophene-(S-oxide)

[6-methoxy-2-(4-isopropoxyphenyl)-3-bromo]benzo[b] thiophene-(S-oxide)

[2-(4-methoxyphenyl)-3-bromo]benzo[b]thiophene-(S-oxide)

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene-(S-oxide)

[3-[4-[2-(1-piperidinyl) ethoxy]phenoxy]-2-(4-methoxyphenyl)] benzo[b]thiophene-(S-oxide)

[6-benzyloxy-2-(4-methoxyphenyl)-3-bromo]benzo[b]thiophene-(S-oxide)

[6-isopropoxy-2-(4-methoxyphenyl)-3-bromo]benzo[b]thiophene-(S-oxide)

[6-methoxy-2-(4-benzyloxyphenyl)-3-bromo]benzo[b]thiophene-(S-oxide)

[6-methoxy-2-(4-isopropoxyphenyl)-3-bromo]benzo[b]thiophene-(S-oxide)

[6-benzyloxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene-(S-oxide)

[6-isopropoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene-(S-oxide)

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene-(S-oxide)

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene-(S-oxide)

[6-methoxy-2-(4-methoxyphenyl)-3-(4-methoxymethyleneoxy) thiophenoxy]benzo[b]thiophene

[6-methoxy-2-(4-methoxyphenyl)-3-(4-hydroxy)thiophenoxy] benzo[b]thiophene

Group II:

[3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)] benzo[b]thiophene

3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)] benzo[b]thiophene hydrochloride

[3-[4-[2-(1-pyrolidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)] benzo[b]thiophene

[3-[4-[2-(1-hexamethyleneimino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[3-[4-[2-(1-N,N-diethylamino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)] benzo[b]thiophene hydrochloride

[3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(phenyl)]benzo [b]thiophene hydrochloride

[3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-fluorophenyl)] benzo[b]thiophene

[6-methoxy-2-(4-methoxyphenyl)-3-(4-benzyloxy)phenoxy]-benzo[b]thiophene

[6-isopropoxy-2-(4-methoxyphenyl)-3-(4-benzyloxy)phenoxy]-benzo[b]thiophene

[6-methoxy-2-(4-isopropoxyphenyl)-3-(4-benzyloxy)phenoxy]-benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-pyrolodinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydro-
chloride

[6-methoxy-3-[4-[2-(1-N,N-diethylamino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene   hydro-
chloride

[6-methoxy-3-[4-[2-(morpholino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[3-(piperidino)propoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[3-(1-N,N-diethylamino)propoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene oxalate

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-pyrolidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-N,N-diethylamino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(morpholino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[3-(1-N,N-diethylamino)propoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-N,N-diisopropylamino)-ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[3-(piperidino)propoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-benzyloxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-benzyloxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-benzyloxy-3-[4-[2-(1-hexamethylimino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-benzyloxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-benzyloxy-3-[4-[2-(1-morpholino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxyoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxy-3-[4-[2-(1-hexamethylimino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxy-3-[4-[2-(1-morpholino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-hexamethylimino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-morpholino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-hexamethylimino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-morpholino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]phenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]phenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-morpholino)ethoxy]phenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]phenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]phenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-morpholino)ethoxy]phenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]phenoxy]-2-(4-hydrooxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-morpholino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]phenoxy]-2-(4-hydrooxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-morpholino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-benzoyloxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-benzoyloxyphenyl)]benzo[b]thiophene hydrochloride

[6-ethylsulfonyloxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-ethylsulfonyloxyphenyl)]benzo[b]thiophene

hydrochloride

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-ethylsulfonyloxyphenyl)]benzo[b]thiophene   hydro-
chloride

[6-ethylsulfonyloxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene   hydro-
chloride

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-triflouromethanesulfonyloxyphenyl)]benzo[b]thi-
ophene

3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-benzoyloxyphenyl)]benzo[b]thiophene hydrochloride

3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-pivaloyloxyphenyl)]benzo[b]thiophene hydrochloride

3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-butylsulfonyl-oxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-benzyloxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-benzyloxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-benzyloxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-benzyloxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-benzyloxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]-thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-isopropoxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]-thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-(4-[2-(1-morpholino)ethoxy)thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]-thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]thiophenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]thiophenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-isopropoxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-pyrrolidinyl)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-hexamethyleneimino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-N,N-dimethylamino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[6-hydroxy-3-[4-[2-(1-morpholino)ethoxy]thiophenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-phenyl] benzo[b]thiophene hydrochloride

[0116] The following examples are presented to further illustrate the preparation of compounds of the present invention. It is not intended that the invention be limited in scope by reason of any of the following examples.

[0117] NMR data for the following Examples were generated on a GE 300 MHz NMR instrument, and anhydrous d-6 DMSO was used as the solvent unless otherwise indicated.

Preparation 1

Preparation of [3-[4-(2-(1-piperidinyl)ethoxy]phenoxy] -2-(4-hydroxyphenyl)]benzo[b]thiophene [3-(4-benzyloxy)phenoxy]benzo[b]thiophene

[0118]
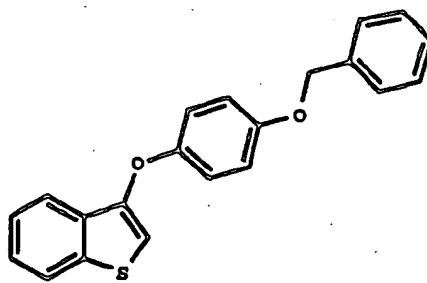
[0119] To a solution of 3-bromo-benzo[b]thiophene (69.62 g, 0.325 mol) in 55 mL of anhydrous collidine under N_2 was added 4-benzyloxyphenol (97.6 g, 0.488 mol) and cuprous oxide (23.3 g, 0.163 mol). The mixture was heated to reflux for 24 hours. Upon cooling, the reaction mixture was diluted with ethyl acetate (200 mL) and the crude mixture filtered through a pad of Celite® (Aldrich, Milwaukee, WI) to remove inorganic salts. The filtrate was washed with 1N hydrochloric acid (3 x 150 mL). The organic was dried (sodium sulfate) and concentrated *in vacuo* to a liquid. Thianaphthene was removed by distillation (10 mm Hg, 115-120° C). The remainder of the material was chromatographed (silicon dioxide, hexanes: ethyl acetate 85:15) to provide 12.2 g of benzo[b]thiophene and 12.95 g (35% based on recovered starting material) of [3-(4-benzyloxy)phenoxy]benzo-[b]thiophene as an off-white solid. mp 84-86° C. ^{1}H NMR (CDCl$_3$) d 7.91-7.83 (m, 2H), 7.47-7.34 (m, 7H), 7.04 (q, J$_{AB}$ = 9.0 Hz, 4H), 6.47 (s, 1H), 5.07 (s, 2H). *Anal.* Calcd. for C$_{21}$H$_{16}$O$_2$S: C, 75.88; H, 4.85. Found: C, 75.75; H, 5.00.

Preparation 2

[2-Iodo-3-(4-benzyloxy)phenoxy]benzo-[b]thiophene

5   **[0120]**
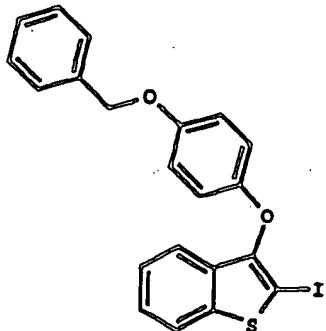
20

[0121] To a solution of [3-(4-benzyloxy)phenoxy]benzo[b] thiophene (6.00 g, 18.1 mmol) in anhydrous tetrahydro-
furan (100 mL) under N_2 at -78° C was added n-butyllithium (12.4 mL, 19.9 mmol, 1.6 M in hexanes) dropwise via
syringe. The solution turned from colorless to deep orange. After stirring for 20 minutes at -78° C, the lithio species
was treated with I_2 (5.03, 19.9 mmol), added dropwise via canula as a solution in 50 mL of anhydrous tetrahydrofuran.
25   Upon completion of the addition, the reaction turned light yellow in color, and was allowed to slowly warm to room
temperature. The reaction was quenched by the addition of 0.1 N sodium sulfite solution (200 mL). The layers were
separated and the aqueous extracted with ethyl acetate (2 x 150 mL). The organic was combined, dried (sodium
sulfate), and concentrated *in vacuo* to give an oil that crystallized on standing. Recrystallization from hexanes/ethyl
ether yielded 7.10 g (86%) of [2-Iodo-3-(4-benzyloxy)phenoxy]benzo[b] thiophene as a white crystalline powder. mp
30   87-92° C. ^{1}H NMR (CDCl$_3$) d 7.72 (d, J = 8.1 Hz, 1H), 7.47-7.20 (m, 8H), 6.89 (s, 4H), 5.01 (s, 2H). *Anal.* Calcd. for
$C_{21}H_{15}O_2SI$: C, 55.03; H, 3.30. Found: C, 55.29; H, 3.31.

Preparation 3

35   **[2-(4-tertbutyloxyphenyl)-3-(4-benzyloxy)phenoxy] benzo[b]thiophene**

[0122]

40
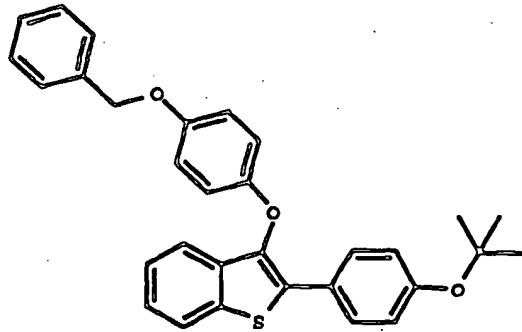
50

[0123] To a solution of [2-Iodo-3-(4-benzyloxy)phenoxy]-benzo[b]thiophene (4.50 g, 9.82 mmol) in toluene (20 mL)
was added 4-(tertbutoxy)phenyl boronic acid (2.28 g, 11.75 mmol) followed by tetrakistriphenylphosphinepalladium
55   (0.76 g, 0.66 mmol). To this solution was added 14.5 mL of 2N sodium carbonate solution. The resulting mixture was
heated to reflux for 3 hours. Upon cooling, the reaction was diluted with 150 mL of ethyl acetate. The organic was
washed with 0.1N sodium hydroxide (2 x 100 mL) and then dried (sodium sulfate). Concentration produced a semi-
solid that was dissolved in chloroform and passed through a pad of silicon dioxide. Concentration produced an oil that

was triturated from hexanes to yield 4.00 g (91%) of [2-(4-tertbutyloxyphenyl)-3-(4-benzyloxy)phenoxy]benzo[b]thiophene as a white powder. mp 105-108° C. ^{1}H NMR (CDCl$_3$) d 7.77 (d, J = 7.7 Hz, 1H), 7.68 (d, J = 8.6 Hz, 2H), 7.43-7.24 (m, 8H), 6.98 (d, J = 8.6 Hz, 2H), 6.89 (q, J$_{AB}$ = 9.3 Hz, 4H), 4.99 (s, 2H), 1.36 (s, 9H). FD mass spec: 480. *Anal.* Calcd. for C$_{31}$H$_{28}$O$_3$S: C, 77.47; H, 5.87. Found: C, 77.35; H, 5.99.

Preparation 4

Prepared in a similar manner employing 4-methoxyphenylboronic acid was [2-(4-methoxyphenyl)-3-(4-benzyloxy)phenoxy]benzo[b]-thiophene

[0124]
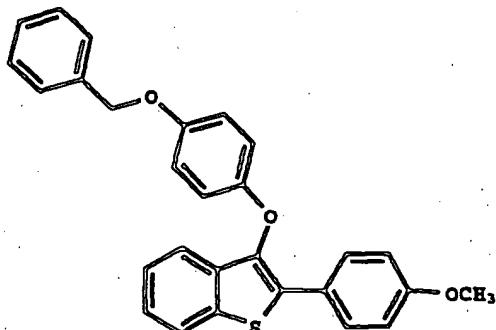
[0125]   Yield = 73%. mp = 115-118° C. ^{1}H NMR (CDCl$_3$) d 7.80-7.90 (m, 3H), 7.33-7.53 (m, 8H), 6.93-7.06 (m, 6H), 5.00 (s, 2H), 3.83 (s, 3H). FD mass spec: 438. *Anal.* Calcd. for C$_{28}$H$_{22}$O$_3$S: C, 76.69; H, 5.06. Found: C, 76.52; H, 5.09.

Preparation 5

[2-(4-tertbutyloxyphenyl)-3-(4-hydroxy)phenoxy] benzo[b]thiophene

[0126]
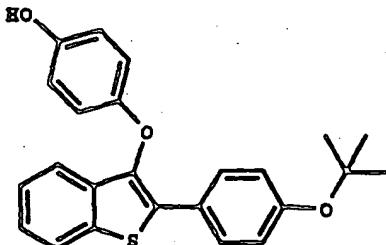
[0127]   To a solution of [2-(4-tertbutyloxyphenyl)-3-(4-benzyloxy)phenoxy]benzo[b]thiophene (1.50 g, 3.37 mmol) in 30 mL of absolute ethanol containing 1% concentrated hydrochloric acid was added 0.50 g of 10% palladium-on-carbon. The mixture was hydrogenated at 40 psi for 1 hour, after which the reaction was judged to be complete by thin layer chromatography. The mixture was filtered through a pad of Celite, and the filtrate concentrated *in vacuo.* The crude product was dissolved in minimal ethyl acetate and passed through a short silicon dioxide column to remove Celite (ethyl acetate as eluant). Concentration provided a white solid that was triturated from hexanes/ethyl ether. Filtration provided 868 mg (73%) of [2-(4-tertbutyloxyphenyl)-3-(4-hydroxy)phenoxy]-benzo[b]thiophene. mp 210-213° C. ^{1}H NMR (DMSO-d_6) d 9.13 (s, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.35-7.26 (m, 3H), 7.01 (d, J = 8.6 Hz, 2H), 6.70 (q, J$_{AB}$ = 8.9 Hz, 4H), 1.28 (s, 9H). FD mass spec: 390. *Anal.* Calcd. for C$_{24}$H$_{22}$O$_3$S: C, 73.82; H, 5.68. Found: C, 73.98; H, 5.84.

Preparation 6

**Prepared in a similar manner was [2-(4-methoxyphenyl)-3-(4-hydroxy)phenoxy]benzo[b]thiophene**

5   [0128]
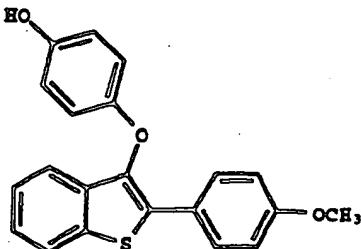
[0129]   Yield = 80%. mp = 120-125° C. ^{1}H NMR (CDCl$_3$) d 7.80-7.90 (m, 3H), 7.48 (m, 1H), 7.30-7.48 (m, 2H),
6.90-7.03 (m, 4H), 6.76-6.86 (m, 2H), 3.82 (s, 3H). FD mass spec: 348; *Anal* Calcd. for C$_{21}$H$_{16}$O$_3$S: C, 72.39; H, 4.63.
20   Found: C, 72.68; H, 4.82.

Example 1

[3-(4-(2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

25

[0130]
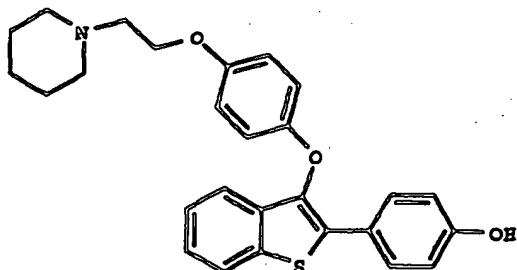
40   [0131]   To a solution of [2-(4-tertbutyloxyphenyl)-3-(4-hydroxy) phenoxy]benzo[b]thiophene (1.25 g, 3.20 mmol) in
anhydrous N,N-dimethylformamide (10 mL) at ambient temperature was added cesium carbonate (5.70 g, 17.6 mmol).
After stirring for 20 minutes, 2-chloroethylpiperidine hydrochloride (1.95 g, 10.56 mmol) was added in small portions.
The resulting heterogeneous mixture was stirred vigorously for 24 hours. The contents of the reaction were then diluted
with water (200 mL). The aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic layer
45   was then washed with water (2 x 200 mL). Drying of the organic layer (sodium sulfate) and concentration *in vacuo*
gave an oil. Chromatography (5-10% methanol/chloroform) provided 1.47 g (91%) of 3-[4-[2-(1-piperidinyl)ethoxy]phe-
noxy]-2-(4-tertbutyloxyphenyl)]benzo[b]-thiophene that was carried on directly to the next step without characterization.
[0132]   3-[4-[2-(1-piperidinyl)ethoxy]phenoxy] -2-(4-tertbutyloxy-phenyl)]benzo[b]thiophene (1.37 g, 2.73 mmol) was
dissolved in triflouroacetic acid (10 mL) at ambient temperature. After stirring for 15 minutes, the solvent was removed
50   *in vacuo*. The residue was dissolved in ethyl acetate (20 mL) and washed with sat. sodium bicarbonate solution (3 x
10 mL). The organic layer was dried (sodium sulfate) and concentrated whereupon a white solid precipitated formed
in solution. The product was recrystallized from ethyl acetate-ethyl ether to provide 1.03 g (85%) of 3-[4-[2-(1-piperidinyl)
ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]-thiophene as colorless crystals. mp 169-172° C. ^{1}H NMR (DMSO-d_6)
d 9.81 (s, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.36-7.26 (m, 3H), 6.86 (s, 4H), 6.78 (d, J = 8.6 Hz,
55   2H), 4.10 (m, 2H), 3.29 (m, 2H), 2.95-2.75 (m, 4H), 1.68-1.40 (m, 6H). *Anal.* Calcd. for C$_{27}$H$_{27}$NO$_3$S•0.55 CF$_3$CO$_2$H:
C, 66.40; H, 5.46; N, 2.76. Found: C, 65.99; H, 5.49; N, 2.61

Example 2

3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene was converted to its hydrochloride salt in 90% yield by treatment with ethyl ether•hydrochloric acid in ethyl acetate

[0133]
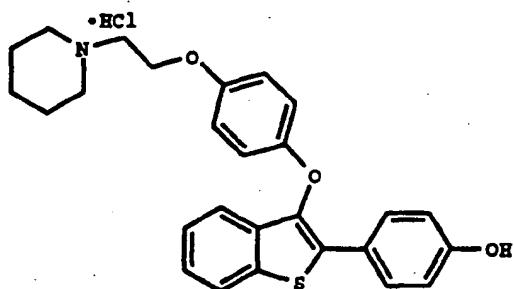
[0134] Data for Example 2 mp 233-240° C. ^{1}H NMR (DMSO-d_6) d 10.43 (m, 1H), 9.89 (s, 1H), 7.93-7.95 (m, 1H), 7.60-7.64 (m, 2H), 7.35-7.50 (m, 3H), 6.83-7.03 (m, 6H), 4.27-4.30 (m, 2H), 3.40-3.60 (m, 4H), 2.96-3.10 (m, 2H), 1.70-1.95 (m, 5H), 1.40-1.53 (m, 1H). FD mass spec: 446. *Anal.* Calcd. for $C_{27}H_{27}NO_3S$•1.0HCl: C, 67.28; H, 5.86; N, 2.91. Found: C, 67,07; H, 5.66; N, 2.96.

Example 3

Prepared in an analogous manner were the following examples:

[0135] [3-[4-[2-(1-pyrolidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene
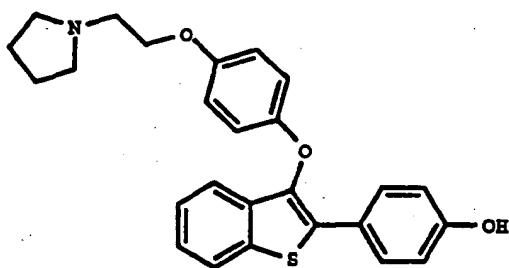

[0136] mp 150-155° C. ^{1}H NMR (DMSO-d_6) d 9.79 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.36-7.26 (m, 3H), 6.84 (s, 4H), 6.78)d, J = 8.6 Hz, 2H), 4.00 (bt, 2H), 2.92 (m, 2H), 2.85 (m, 4H), 1.73 (m, 4H): *Anal.* Calcd. for $C_{26}H_{25}NO_3S$•0.33 CF_3CO_2H: C, 68.25; H, 5.44; N, 2.99. Found: C, 68.29; H, 5.46; N, 3.19.

Example 4

[3-[4-[2-(1-hexamethyleneimino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[0137]
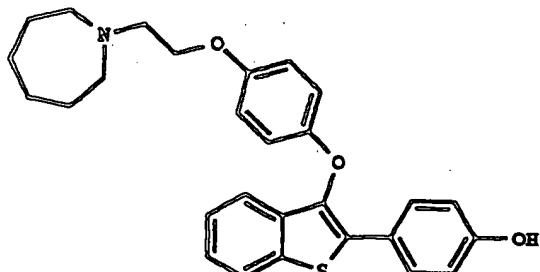
[0138] mp 189-191° C. ^{1}H NMR (DMSO-d_6) d 7.91 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.34-7.25 (m, 3H), 6.81 (s, 4H), 6.75 (d, J = 8.6 Hz, 2H), 3.89 (bt, 2H), 2.75 (bt, 2H), 2.68 (m, 4H), 1.48 (m, 8H). *Anal.* Calcd. for $C_{28}H_{29}NO_3S$°1.50 H_2O: C, 69.11; H, 6.79; N, 2.88. Found: C, 69.25; H, 6.79; N, 2.58.

Example 5

[3-[4-[2-(1-N,N-diethylamino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[0139]
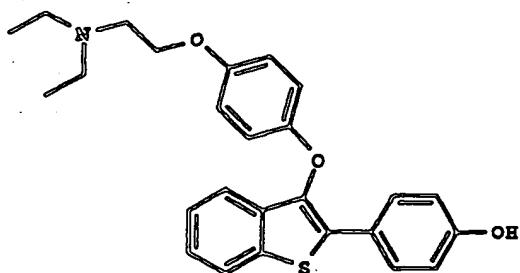
[0140] mp 70° C. ^{1}H NMR (DMSO-d_6) d 9.91 (bs, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.35-7.24 (m, 3H), 6.82 (s, 4H), 6.78 (d, J = 8.6 Hz, 2H), 3.88 (bt, 2H), 2.76 (bt, 2H), 2.51 (m, 4H), 0.91 (m, 6H). FD mass spec: 434. *Anal.* Calcd. for $C_{26}H_{27}NO_3S$°0.50 H_2O: C, 70.56; H, 6.38; N, 3.16 Found: C, 70.45; H, 6.26; N, 3.20.

Example 6

3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

5 **[0141]**
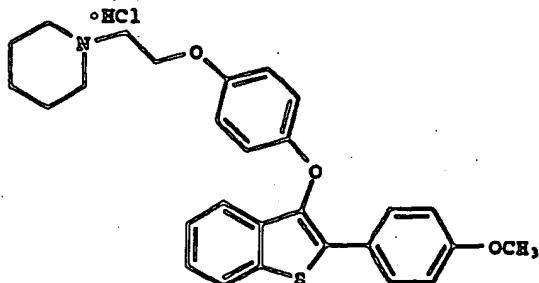
[0142] mp = 228-230° C. ^{1}H NMR (DMSO-d_6) d 7.96 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.35-7.50 (m, 3H), 6.98 (d, J = 8.7 Hz, 2H), 6.86-6.90 (m, 4H), 4.28-4.31 (m, 2H), 3.74 (s, 3H), 3.37-3.45 (m, 4H), 2.92-2.96 (m, 2H), 2.46-2.48 (m, 5H), 1.74 (m, 1H). FD mass spec: 459. *Anal* Calcd. for $C_{28}H_{29}NO_3S\cdot1.0HCl$: C, 67.80; H, 6.10; N, 2.82. Found: C, 68.06; H, H, 6.38; N, 2.60.

Alternate Synthesis of [2-(4-tertbutyloxyphenyl)-3-(4-benzyloxy)phenoxy]benzo[b]thiophene

Preparation 7

**[3-(4-benzyloxy)phenoxy]benzo[b]thiophene-2-boronic acid**

30 **[0143]**
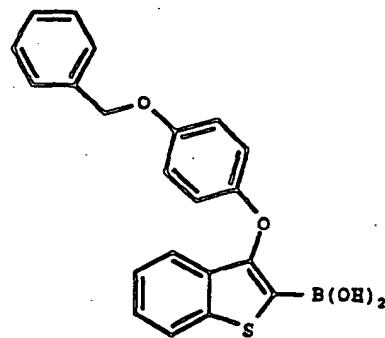
[0144] To a -78° C solution of [3-(4-benzyloxy)phenoxy]benzo [b]-thiophene (5.00 g, 15.1 mmol) in 20 mL of anhydrous tetrahydrofuran under N_2 was added n-butyllithium (9.90 mL, 15.8 mmol, 1.6 M in hexanes) dropwise via syringe. After stirring for 15 minutes, B(OiPr)$_3$ (3.83 mL, 16.6 mmol) was added via syringe, and the resulting mixture was allowed to warm to 0° C. The reaction was then quenched by distributing between ethyl acetate and 1.0N hydrochloric acid (100 mL each). The layers were separated and the organic was extracted with water (1 x 100 mL). The organic layer was dried (sodium sulfate) and concentrated *in vacuo* to a solid that was triturated from ethyl ether/hexanes. Filtration provided 3.96 g (70%) of [3-(4-benzyloxy)phenoxy] benzo[b]thiophene-2-boronic acid as a white solid. mp 115-121° C. ^{1}H NMR (DMSO-d_6) d 8.16 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.42-7.23 (m, 7H), 6.90 (q, J$_{AB}$ = 9.0 Hz, 4H), 5.01 (s, 2H). *Anal.* Calcd. for $C_{21}H_{17}O_4SB$: C, 67 04; H, 4.55. Found: C, 67.17; H, 4.78.

[0145] [3-(4-Benzyloxy)phenoxy]benzo[b]thiophene-2-boronic acid was reacted with 4-(-tertbutoxy)bromobenzene according to the conditions described above for [2-iodo-3-(4-benzyloxy) phenoxy]-benzo[b]thiophene and 4-(tertbutoxy)phenyl boronic acid to give [2-(4-tertbutyloxyphenyl)-3-(4-benzyloxy)phenoxy]benzo[b] thiophene in 81% yield.

[0146] Examples prepared by employing this method are:

Example 7

[3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(phenyl)]benzo [b]thiophene hydrochloride

[0147]
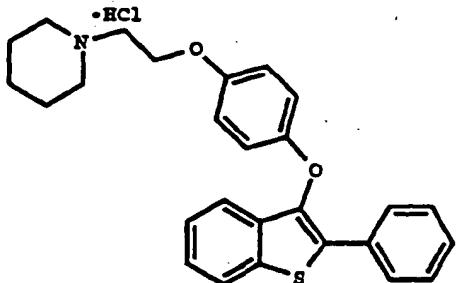
[0148]   mp 223-226° C. ^{1}H NMR (DMSO-d_6) d 7.99 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 7.3 Hz, 1H), 7.44-7.30 (m, 7H), 6.90 (s, 4H), 4.27 (m, 2H), 3.43-3.35 (m, 4H), 2.97-2.88 (m, 2H), 1.73-1.61 (m, 5H), 1.34 (m, 1H). *Anal.* Calcd. for $C_{27}H_{27}NO_2S$•1.0 HCl: C, 69.59; H, 6.06; N, 3.00. Found: C, 69.88; H, 6.11; N, 3.19.

Example 8

[3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-flourophenyl)]benzo[b]thiophene

[0149]
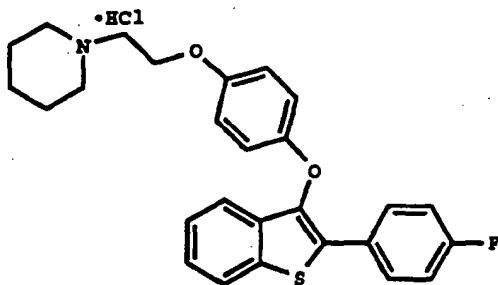
[0150]   mp 219-226° C. ^{1}H NMR (DMSO-d_6) d 10.20 (bs, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.77-7.73 (m, 4H), 7.42-7.25 (m, 5H), 6.90 (s, 4H), 4.27 (m, 2H), 3.44-3.31 (m, 4H), 2.96-2.89 (m, 2H), 1.78-1.61 (m, 5H), 1.34 (m, 1H). FD mass spec: 447. *Anal.* Calcd. for $C_{27}H_{26}NO_2SF$•1.0 HCl: C, 67.00; H, 5.62; N, 2.89. Found: C, 67.26; H, 5.67; N, 3.03.

Preparation 8

Synthesis of [6-Hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[6-methoxy-2-(4-methoxyphenyl)-3-bromo]benzo-[b]thiophene

[0151]
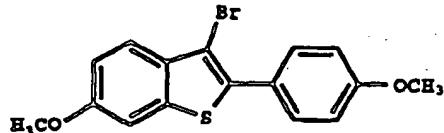
[0152]   To a solution of [6-methoxy-2-(4-methoxyphenyl)]benzo [b]thiophene (27.0 g, 100 mmol)in 1.10 L of chloroform at 60° C was added bromine (15.98 g, 100 mmol) dropwise as a solution in 200 mL of chloroform. After the addition was complete, the reaction was cooled to room temperature, and the solvent removed *in vacuo* to provide 34.2 g (100%) of [6-methoxy-2-(4-methoxyphenyl)-3-bromo]benzo[b]thiophene as a white solid. mp 83-85° C. ^{1}H NMR (DMSO-d_6) d 7.70-7.62 (m, 4H), 7.17 (dd, J = 8.6, 2.0 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H). FD mass spec: 349, 350. *Anal.* Calcd. for $C_{16}H_{13}O_2SBr$: C, 55.03; H, 3.75. Found: C, 54.79; H, 3.76.

Example 9

[6-methoxy-2-(4-methoxyphenyl)-3-(4-benzyloxy) phenoxy]-benzo[b]thiophene

[0153]
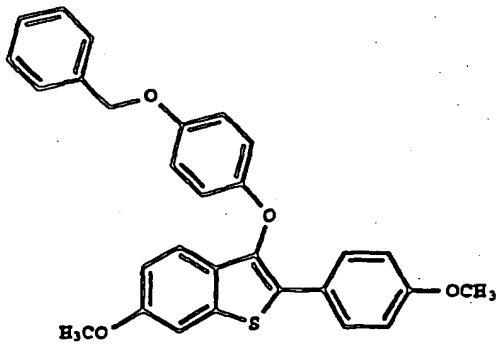
[0154]   To a solution of [6-methoxy-2-(4-methoxyphenyl)-3-bromo] benzo[b]thiophene (34.00 g, 97.4 mmol) in 60 mL of collidine under N_2 was added 4-benzyloxyphenol (38.96 g, 194.8 mmol) and cuprous oxide (14.5 g, 97.4 mmol). The resultant mixture was heated to reflux for 48 hours. Upon cooling to room temperature, the mixture was dissolved in acetone (200 mL), and the inorganic solids were removed by filtration. The filtrate was concentrated *in vacuo*, and the residue dissolved in methylene chloride (500 mL). The methylene chloride solution was washed with 3N hydrochloric acid (3 X 300 mL), followed by 1N sodium hydroxide (3 x 300 mL). The organic layer was dried (sodium sulfate), and concentrated *in vacuo*. The residue was taken up in 100 mL of ethyl acetate whereupon a white solid formed that was collected by filtration [recovered [6-methoxy-2-(4-methoxyphenyl)]benzo-[b]thiophene (4.62 g, 17.11 mmol]. The filtrate was concentrated *in vacuo*, and then passed through a short pad of silica gel (methylene chloride as eluant) to remove baseline material. The filtrate was concentrated *in vacuo*, and the residue crystallized from hexanes/ethyl acetate to provide initially 7.19 g of [6-methoxy-2-(4-methoxyphenyl)-3-(4-benzyloxy)phenoxy]benzo[b]-thiophene as an off-white crystalline solid. The mother liquor was concentrated and chromatographed on silica gel (hexanes/ethyl acetate 80: 20) to provide an additional 1.81 g of product. Total yield of [6-methoxy-2-(4-methoxyphenyl)-3-(4-benzyloxy)phenoxy]-benzo[b]thiophene was 9.00 g (24% based on recovered starting material). The basic extract was acidified to pH = 4 with 5N hydrochloric acid, and the resultant precipitate collected by filtration and dried to give 13.3 g of recovered

4-benzyloxyphenol. mp 100-103° C. ^{1}H NMR (CDCl$_3$): d 7.60 (d, J = 8.8 Hz, 2H), 7.39-7.24 (m, 7H), 6.90-6.85 (m, 7H), 4.98 (s, 2H), 3.86 (s, 3H) 3.81 (s, 3H). FD mass spec: 468. *Anal.* Calcd. for C$_{29}$H$_{24}$O$_4$S: C, 74.34; H, 5.16. Found: C, 74.64; H, 5.29.

Preparation 9

**[6-methoxy-2-(4-methoxyphenyl)-3-(4-hydroxy)-phenoxy]benzo[b]thiophene**

[0155]
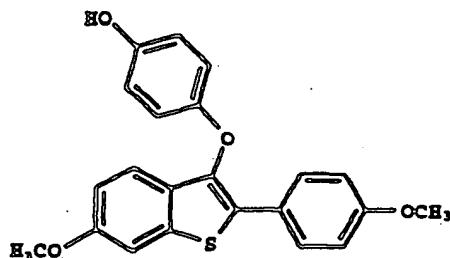
[0156] To a solution of [6-methoxy-2-(4-methoxyphenyl)-3-(4-benzyloxy)phenoxy]benzo[b]thiophene (1.50 g, 3.20 mmol) in 50 mL of ethyl acetate and 10 mL of 1% concentrated hydrochloric acid in ethanol was added 10% palladium-on-carbon (300 mg). The mixture was hydrogenated at 40 psi for 20 minutes, after which time the reaction was judged complete by thin layer chromatography. The mixture was passed through Celite to remove catalyst, and the filtrate concentrated *in vacuo* to a white solid. The crude product was passed through a pad of silica gel (chloroform as eluant). Concentration provided 1.10 g (91%) of [6-methoxy-2-(4-methoxyphenyl)-3-(4-hydroxy)phenoxy]benzo[b]-thiophene as a white solid. mp 123-126° C. ^{1}H NMR (DMSO-d_6) d 9.10 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 2.1 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 6.89 (dd, J = 8.8, 2.1 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 6.63 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 3.72 (s, 3H). FD mass spec: 378. *Anal.* Calcd. for C$_{22}$H$_{18}$O$_4$S: C, 69.82; H, 4.79. Found: C, 70.06; H, 4.98.

Example 10

[6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene.

[0157]
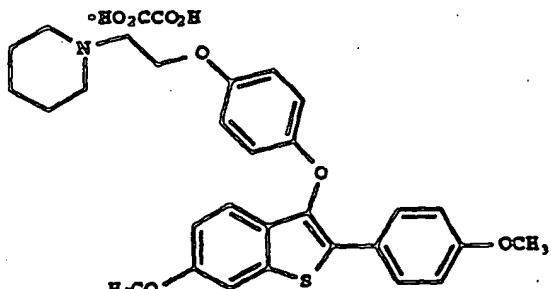
[0158] To a solution of [6-methoxy-2-(4-methoxyphenyl)-3-(4-hydroxy)phenoxy]benzo[b]thiophene (1.12 g, 2.97 mmol) in 7 mL of anhydrous N,N-dimethylformamide under N$_2$ was added cesium carbonate (3.86 g, 11.88 mmol). After stirring for 10 minutes, 2-chloroethylpiperidine hydrochloride (1.10 g, 1.48 mmol) was added. The resultant mixture was stirred for 18 hours at ambient temperature. The reaction was the distributed between chloroform/water (100 mL each). The layers were separated and the aqueous extracted with chloroform (3 x 50 mL). The organic was combined and washed with water (2 x 100 mL). Drying of the organic (sodium sulfate) and concentration provided an oil that was chromatographed on silica gel (2% methanol/chloroform). The desired fractions were concentrated to an oil that was

dissolved in 10 mL of ethyl acetate and treated with oxalic acid (311 mg, 3.4 mmol). After stirring for 10 minutes, a white precipitate formed and was collected by filtration and dried to provide 1.17 g (70%) overall of [6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-methoxyphenyl)]benzo[b] thiophene as the oxalate salt. mp 197-200° C (dec). ^{1}H NMR (DMSO-d_6) d 7.60 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 1.1 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.91 (dd, J = 8.8, 1.1 Hz, 1H), 6.87 (s, 4H), 4.19 (broad t, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.32 (broad t, 2H), 3.12-3.06 (m, 4H), 1.69-1.47 (m, 4H), 1.44-1.38 (m, 2H). FD mass spec: 489 . Anal. Calcd. for $C_{29}H_{31}NO_4S\cdot0.88$ HO_2CCO_2H: C, 64.95; H, 5.80; N, 2.46. Found: C, 64.92; H, 5.77; N, 2.54.

Example 11

Treatment of free base with ethyl ether-hydrochloric acid provided [6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[0159]
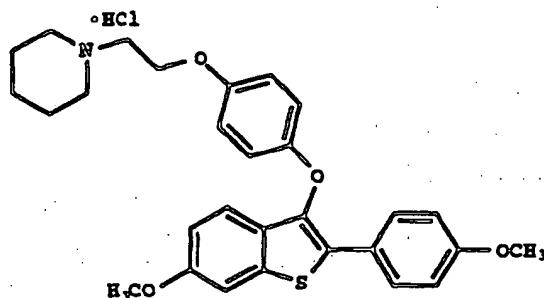
[0160]   mp 216-220° C. ^{1}H NMR (DMSO-d_6) d 10.20 (bs, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 1.5 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 8.7 Hz, 1H), 6.96 (dd, J = 9.0, 1.5 Hz, 1H), 6.92 (q, J_{AB} = 9.0 Hz, 4H), 4.31 (m, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.43 (m, 4H), 2.97 (m, 2H), 1.77 (m, 5H), 1.37 (m, 1H). FD mass spec: 489 . Anal. Calcd. for $C_{29}H_{31}NO_4S\cdot1.0$ HCl: C, 66.21; H, 6.13; N, 2.66. Found: C, 66.,46; H, 6.16; N, 2.74.

Prepared in an analogous manner were the following examples:

Example 12

[6-Methoxy-3-[4-[2-(1-pyrolodinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[0161]
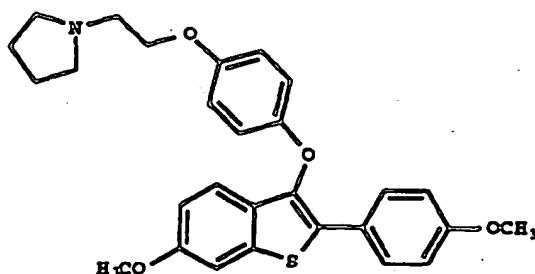
[0162]   mp 95-98° C. ^{1}H NMR (DMSO-d_6) d 7.64 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.94 (dd, J = 9.0, 2.0 Hz, 1H), 6.86 (s, 4H), 3.97 (t, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 2.73 (t, J = 6.0 Hz, 2H), 2.51 (m, 4H), 1.66 (m, 4H). FD mass spec: 477. Anal. Calcd. for $C_{28}H_{29}NO_4S$: C, 70.71; H, 6.15; N, 2.99. Found: C, 70.59; H, 6.15; N, 3.01.

Example 13

**[6-Methoxy-3-[4-[2-(1-hexamethyleneimino)ethoxy] phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride**

[0163]
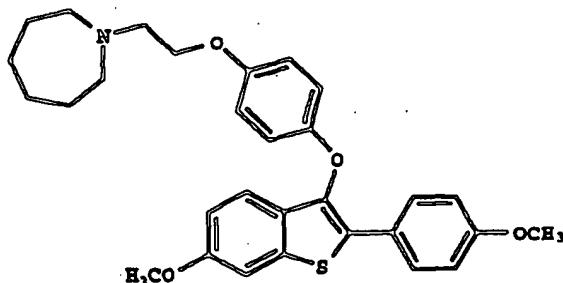
[0164] mp 189-192° C. ^{1}H NMR (DMSO-d_6) d 10.55 (bs, 1H), 7.64 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.95 (dd, J = 9.0, 2.0 Hz, H), 6.86 (s, 4H), 3.94 (t, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 2.80 (t, J = 6.0 Hz, 2H), 2.66 (m, 4H), 1.53 (m, 8H). *Anal.* Calcd. for $C_{30}H_{33}NO_4S$∘1.0 HCl: C, 66.71; H, 6.35; N, 2.59. Found: C, 66.43; H, 6.46; N, 2.84.

Example 14

[6-Methoxy-3-[4-[2-(1-N,N-diethylamino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride
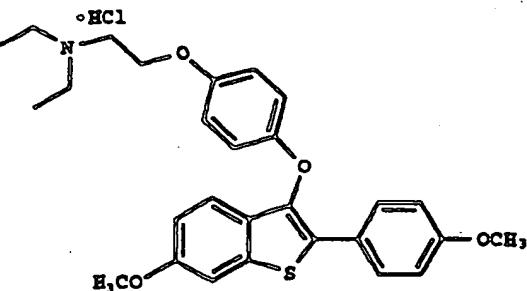
[0165]

[0166] mp 196-198° C. ^{1}H NMR (DMSO-d_6) d 10.48 (bs, 1H), 7.64 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.97 (dd, J = 9.0, 2.0 Hz, 1H), 6.87 (q, J_{AB} = 9.0 Hz, 4H), 4.25 (m, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.54 (m, 2H), 3.09 (m, 4H), 2.00 (m, 3H), 1.88 (m, 3H). *Anal.* Calcd. for $C_{28}H_{31}NO_4S$∘1.5 HCl: C, 63.18; H, 6.15; N, 2.63. Found: C, 63.46; H, 5.79; N, 2.85.

44

Example 15

[6-Methoxy-3-[4-[2-(morpholino)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

5 **[0167]**
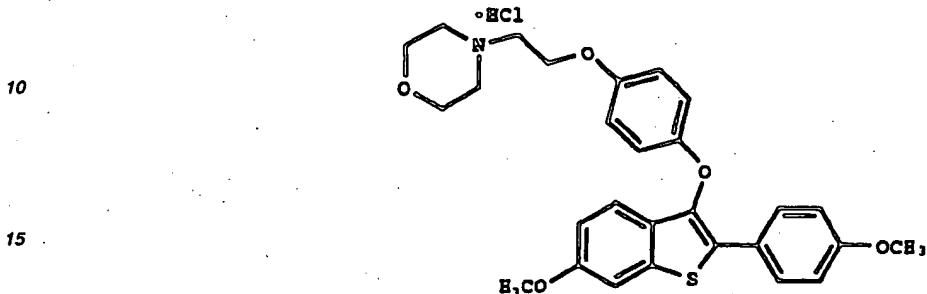
[0168] mp 208-211° C. ^{1}H NMR (DMSO-d_6) d 10.6 (bs, 1H), 7.63 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 2.0 Hz, 1H), 7.20
20 (J = 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.97 (dd, J = 9.0, 2.0 Hz, 1H), 6.91 (q, J_{AB} = 9.0 Hz, 4H), 4.29 (m, 2H),
4.08-3.91 (m, 4H), 3.82 (s, 3H), 3.77 (s, 3H), 3.59-3.42 (m, 4H), 3.21-3.10 (m, 2H). *Anal.* Calcd. for $C_{28}H_{29}NO_5S$·1.0
HCl: C, 63.09; H, 5.73; N, 2.65. Found: C, 63.39; H, 5.80; N, 2.40.

Example 16

25

[6-Methoxy-3-[4-[3-(piperidino)propoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[0169]
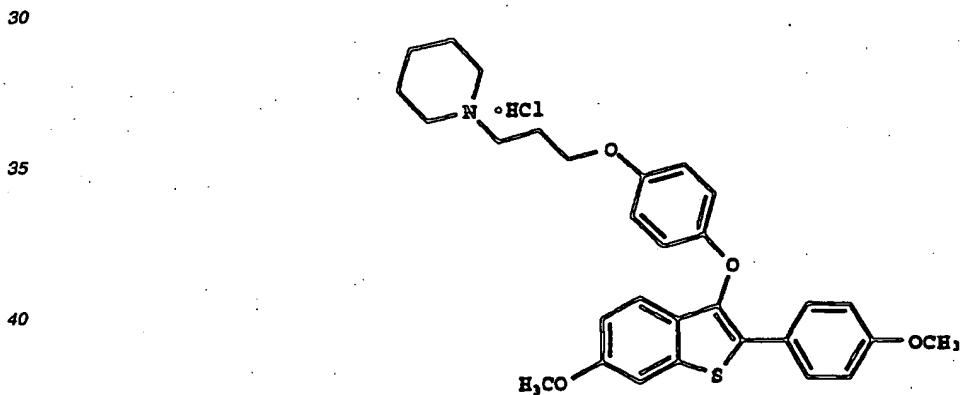
45 **[0170]** mp 195-200° C. ^{1}H NMR (DMSO-d_6) d 9.90 (bs, 1H), 7.64 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 2.0 Hz, 1H), 7.18
(d, J = 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.95 (dd, J = 9.0, 2.0 Hz, 1H), 6.88 (s, 4H), 3.97 (t, J = 6.0 Hz, 2H), 3.83
(s, 3H), 3.77 (s, 3H), 3.44 (m, 2H), 3.15 (m, 2H), 2.87 (m, 2H), 2.12 (m, 2H), 1.77 (m, 5H), 1.39 (m, 1H). *Anal.* Calcd.
for $C_{30}H_{33}NO_4S$·1.15 HCl: C, 66.01; H, 6.40; N, 2.73. Found: C, 66.01; H, 6.40; N, 2.73.

Example 17

**[6-Methoxy-3-[4-[3-(1-N,N-diethylamino)propoxy]phenoxy]-2-(4-methoxyphenyl)] benzo[b]thiophene hydrochloride**

[0171]
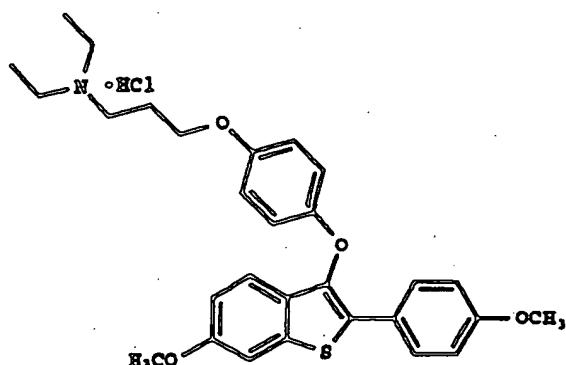
[0172] mp 164-166° C. ¹H NMR (DMSO-d_6) d 9.77 (bs, 1H), 7.64 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 6.95 (dd, J = 9.0, 2.0 Hz, 1H), 6.89 (s, 4H), 3.99 (t, J = 6.0 Hz,2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.15 (m, 6H), 2.06 (m, 2H), 1.20 (t, J = 7.0 Hz, 6H). *Anal.* Calcd. for $C_{29}H_{33}NO_4S$°1.0 HCl: C, 65.96; H, 6.49; N, 2.65. Found: C, 66.25; H, 6.64; N, 2.84.

Example 18

[6-Hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[0173]
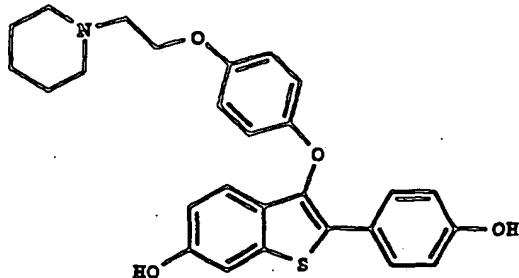
[0174] [6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride (10.00 g, 19.05 mmol) was dissolved in 500 mL of anhydrous methylene chloride and cooled to 8° C. To this solution was added boron tribromide (7.20 mL, 76.20 mmol). The resultant mixture was stirred at 8° C for 2.5 hours. The reaction was quenched by pouring into a stirring solution of saturated sodium bicarbonate (1 L), cooled to 0° C. The methylene chloride layer was separated, and the remaining solids were dissolved in methanol/ethyl acetate. The aqueous layer was then extracted with 5% methanol/ethyl acetate (3 x 500 mL). All of the organic extracts (ethyl acetate and methylene chloride) were combined and dried (sodium sulfate). Concentration *in vacuo* provided a tan solid that was chromato-graphed (silicon dioxide, 1-7% methanol/chloroform) to provide 7.13 g (81 %) of [6-hydroxy-3-[4-[2-(1-piperidinyl) ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]-thiophene as a white solid. mp 93° C. ¹H NMR (DMSO-d_6) d 9.73 (bs, 1H), 9.68 (bs, 1H), 7.45 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 1.8 Hz, 1H), 7.04 (d, J= 8.6 Hz, 1H), 6.84 (dd, J = 8.6, 1.8 Hz, 1H (masked)), 6.81 (s, 4H), 6.75 (d, J = 8.6 Hz, 2H), 3.92 (t, J = 5.8 Hz, 2H), 2.56 (t, J = 5.8 Hz, 2H), 2.36 (m. 4H), 1.43 (m, 4H), 1.32 (m, 2H). FD mass spec: 462. *Anal.* Calcd. for $C_{27}H_{27}NO_4S$: C, 70.20; H, 5.90; N, 3.03. Found: C,

69.96; H, 5.90; N, 3.14.

Example 19

[6-Hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene is converted to its oxalate salt in 80% yield by the procedure described above. Data for [6-hydroxy-3-[4-[2-(1-piperidinyl)-ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene oxalate

[0175]
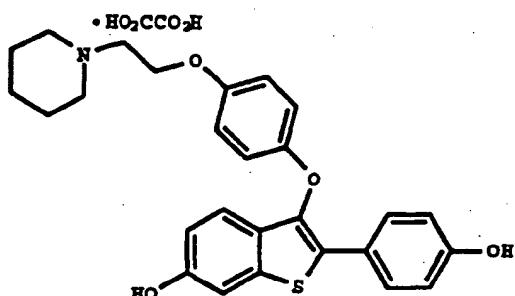
[0176]   mp 246-249° C (dec). ^{1}H NMR (DMSO-d_6) d 7.45 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 1.8 Hz, 1H), 7.05 (d, J = 8.6 Hz, 1H), 6.87 (dd, J = 8.6, 1.8 Hz, 1H (masked)), 6.84 (s, 4H), 6.75 (d, J = 8.6 Hz, 2H), 4.08 (bt, 2H), 3.01 (bt, 2H), 2.79 (m, 4H), 1.56 (m, 4H), 1.40 (m, 2H). FD mass spec 462. Anal. Calcd. for $C_{27}H_{27}NO_4S$•0.75 HO_2CCO_2H: C, 64.63; H, 5.42; N, 2.64. Found: C, 64.61; H, 5.55; N, 2.62.

Example 20

[6-Hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b] thiophene was converted to its hydrochloride salt in 91% yield by treatment of the free base in ethyl acetate with ethyl ether•hydrochloric acid. Data for [6-hydroxy-3-[4-[2-(1-piperidinyl)ethoxy]-phenoxy]-2-(4-hydroxyphenyl)]benzo [b]thiophene hydrochloride

[0177]
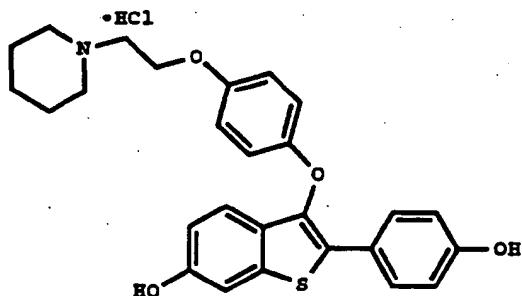
[0178]   mp 158-165° C. ^{1}H NMR (DMSO-d_6) d 9.79 (s, 1H), 9.74 (s, 1H), 7.40 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 2.0 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.86 (q, J_{AB} = 9.3 Hz, 4H), 6.76 (dd, J = 8.6, 2.0 Hz, 1), 6.74 (d, J = 8.6 Hz, 2H), 4.26 (bt, 2H), 3.37 (m, 4H), 2.91 (m, 2H), 1.72 (m, 5 H), 1.25 (m, 1H). FD mass spec 461. Anal. Calcd. for $C_{27}H_{27}NO_4S$•1.0 HCl: C, 65.11; H, 5.67; N, 2.81. Found: C, 64.84; H, 5.64; N, 2.91.

[0179]   Prepared in an analogous manner were the following examples:

Example 21

[6-Hydroxy-3-[4-[2-(1-pyrolidinyl)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene
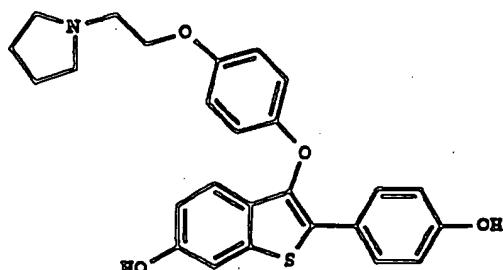
[0180]

[0181] mp 99-113° C. ^{1}H NMR (DMSO-d_6) d 9.75 (s, 1H), 9.71 (s, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 2.0 Hz, 1H), 7.09 (d, J = 9.0 Hz, 1H), 6.85 (s, 1H), 6.80 (dd, J = 9.0, 2.0 Hz, 1H), 6.79 (d, J = 9.0 Hz, 2H), 3.93 (m, 2H), 2.73 (m, 2H), 2.53 (m, 4H), 0.96 (t, J = 7.0 Hz, 4H). *Anal.* Calcd. for $C_{26}H_{25}NO_4S \cdot 0.5 H_2O$: C, 68.40; H, 5.74; N, 3.07. Found: C, 68.52; H, 6.00; N, 3.34.

Example 22

[6-Hydroxy-3-[4-[2-(1-hexamethyleneimino)ethoxy] phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

[0182]
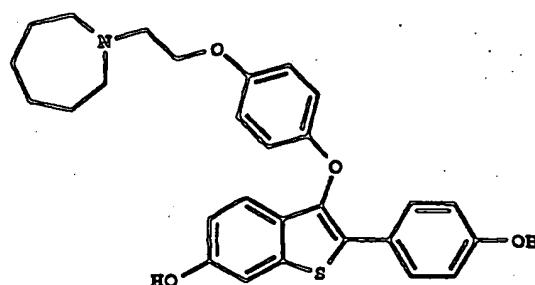
[0183] mp 125-130° C. ^{1}H NMR (DMSO-d_6) d 9.75 (s, 1H), 9.71 (s, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 2.0 Hz, 1H), 7.09 (d, J = 9.0 Hz, 1H), 6.85 (s, 3H), 6.80 (dd, J = 9.0, 2.0 Hz, 1H), 6.79 (d, J = 9.0 Hz), 3.94 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 2.66 (m, 4H), 1.53 (m, 8H). *Anal.* Calcd. for $C_{28}H_{29}NO_4S$: C, 70.71; H, 6.15; N, 2.94. Found: C, 70.67; H, 6.31; N, 2.93.

Example 23

[6-Hydroxy-3-[4-[2-(1-N,N-diethylamino)ethoxy] phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene

5

[0184]

10
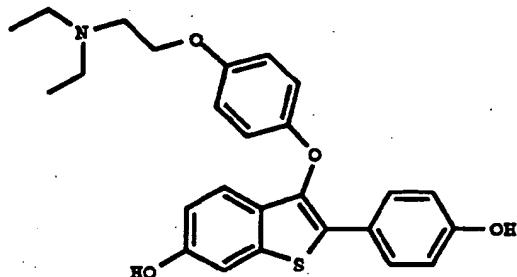
15

[0185] mp 137-141° C. ^{1}H NMR (DMSO-d_6) d 9.75 (s, 1H), 9.71 (s, 1H), 7.49 (d, J = 9.0 Hz, 1H), 7.25 (d, j = 2.0 Hz,
20 1H), 7.09 (d, J = 9.0 Hz, 1H), 6.85 (s, 4H), 6.80 (dd, J = 9.0, 2.0 Hz, 1H), 6.79 (d, J = 9.0 Hz, 2H), 3.95 (t, J = 6.0 Hz,
2H), 2.74 (t, J = 6.0 Hz, 2H), 2.51 (m, 4H), 1.66 (m, 6H). *Anal.* Calcd. for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12.
Found: C, 69.76; H, 5.85; N, 3.40.

Example 24

25

[6-Hydroxy-3-[4-[2-(morpholino)ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[0186]

30

35

40
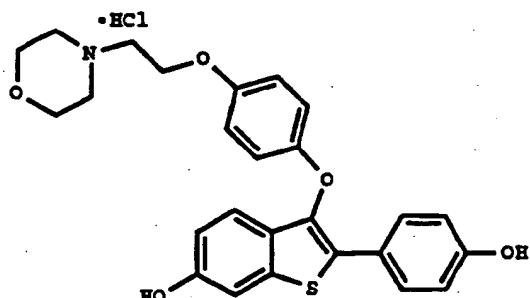
[0187] mp 157-162° C. ^{1}H NMR (DMSO-d_6) d 10.60 (bs, 1H), 9.80 (s, 1H), 9.75 (s, 1H), 7.50 (d, J = 9.0 Hz, 2H),
7.28 (d, J = 2.0 Hz, 1H), 7.10 (d, J = 9.0 Hz, 1H), 6.92 (q, J_{AB} = 9.0 Hz, 4H), 6.81 (dd, J = 9.0, 2.0 Hz, 1H), 6.80 (d, J
45 = 9.0 Hz, 2H), 4.30 (m, 2H), 3.95 (m, 2H), 3.75 (m, 2H), 3.51 (m, 4H), 3.18 (m, 2H). *Anal.* Calcd. for $C_{26}H_{25}NO_5S \cdot HCl$:
C, 62.46; H, 5.24; N, 2.80. Found: C, 69.69; H, 5.43; N, 2.92.

50

55

Example 25

[6-Hydroxy-3-[4-[3-(1-N,N-diethylamino) propoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo [b]thiophene hydrochloride

[0188]
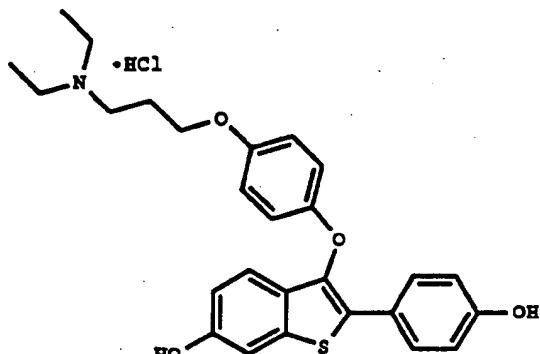
[0189] mp 185-191° C. ^{1}H NMR (DMSO-d_6) d 9.94 (bs, 1H), 9.81 (s, 1H), 9.75 (s, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.27 (dd, J = 2.0 Hz, 1H), 7.10 (d, J = 9.0 Hz, 1H), 6.87 (s, 4H), 6.80 (dd, J = 9.0, 2.0 Hz, 1H), 6.79 (d, J = 9.0 Hz, 2H), 3.99 (t, J = 6.0 Hz, 2H), 3.14 (m, 6H), 2.08 (m, 2H), 1.20 (t, J = 6.0 Hz, 6H). *Anal.* Calcd. for $C_{27}H_{29}NO_4S•1.30HCl$: C, 63.46; H, 5.98; N, 2.74. Found: C, 63.23; H, 6.03; N, 3.14.

Example 26

[6-Hydroxy-3-[4-[2-(1-N,N-diisopropylamino)-ethoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[0190]
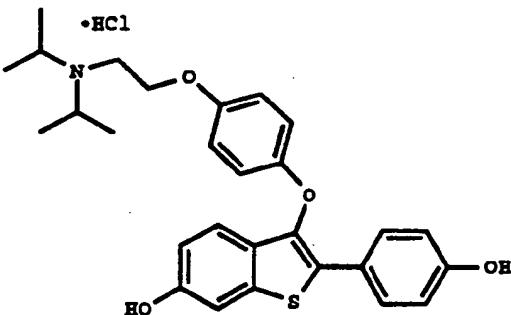
[0191] mp 128-131° C. ^{1}H NMR (DMSO-d_6) d 9.81 (bs, 1H), 9.76 (s, 1H), 9.02 (s, 1H), 7.49 (d, J = 9.0 Hz, 2H), 7.28 (m, 1H), 7.09 (d, J = 9.0 Hz, 1H), 6.90 (s, 4H), 6.79 (m, 3H), 4.19 (m, 2H), 3.68 (m, 2H), 3.50 (m, 2H). 1.31 (m, 12H). *Anal.* Calcd. for $C_{28}H_{31}NO_4S•1.33HCl$: C, 63.92; H, 6.19; N, 2.66. Found: C, 63.82; H, 6.53; N, 2.61.

Example 27

[6-Hydroxy-3-[4-[3-(piperidino)propoxy]phenoxy]-2-(4-hydroxyphenyl)]benzo[b]thiophene hydrochloride

[0192]
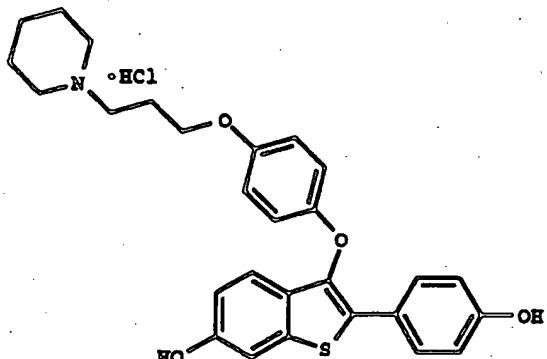
[0193] mp 258-262° C. ^{1}H NMR (DMSO-d_6) d 9.85 (bs, 1H), 9.81 (s, 1H), 9.75 (s, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 2.0 Hz, 1H), 7.10 (d, J = 9.0 Hz, 1H), 6.87 (s, 4H), 6.80 (dd, J = 9.0, 2.0 Hz, 1H), 6.79 (d, J = 9.0 Hz, 2H), 3.97 (t, J = 6.0 Hz, 2H), 3.44 (m, 2H), 3.15 (m, 2H), 2.88 (m, 2H), 2.11 (m, 2H), 1.73 (m, 5H), 1.39 (m, 1H). *Anal.* Calcd. for $C_{28}H_{29}NO_4S\bullet 0.75HCl$: C, 66.87; H, 5.96; N, 2.78. Found: C, 67.04; H, 5.90; N, 2.68.

[0194] Alternatively, as shown in Scheme III, *supra*, Example 19 was prepared using the methoxymethyl (MOM) protecting groups in place of methoxy. The methods are directly analogous to those just described, with the exception that the MOM groups are removed in the final step by acid hydrolysis.

Preparation 10

[6-Methoxy-2-(4-methoxmethyloxyphenyl)-3-(4-benzyloxy) phenoxy]benzo[b]thiophene

[0195]
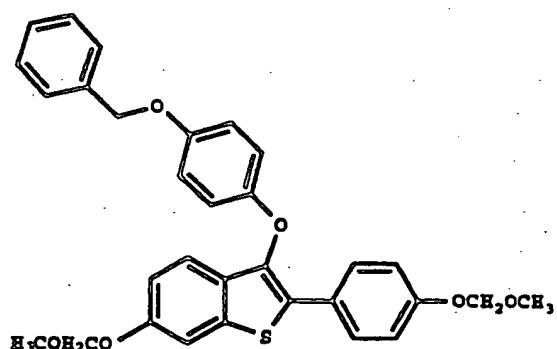
[0196] mp 94-96° C. ^{1}H NMR (DMSO-d_6) d 7.65 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.43-7.32 (m, 5H), 7.23 (d, J = 8.8 Hz, 1H), 7.08 (d, J =8.6 Hz, 2H), 7.04 (dd, J = 8.8, 2.0 Hz, 1H), 6.92 (q, J_{AB} = 9.2 Hz, 4H), 5.26 (s, 2H), 5.21 (s, 2H), 5.01 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H). FD mass spec 528.

Preparation 11

[6-Methoxy-2-(4-methoxmethyloxyphenyl)-3-(4-hydroxy)phenoxy]benzo[b]thiophene

[0197]
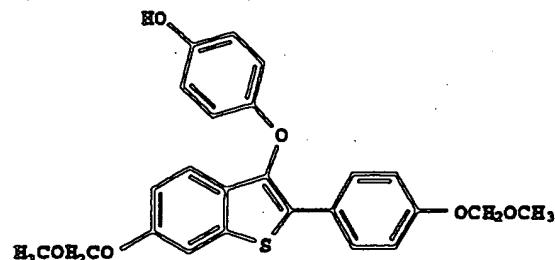
[0198] mp 90-91° C. ^{1}H NMR (DMSO-d_6) d 9.15 (s, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.05 (dd, J = 8.8, 2.0 Hz, 1H), 6.72 (q, J_{AB} = 9.1 Hz, 4H), 5.26 (s, 2H), 5.21 (s, 2H), 3.40 (s, 3H), 3.37 (s, 3H). FD mass spec 438. *Anal.* Calcd. for $C_{24}H_{22}O_6S$: C, 65.74; H, 5.06. Found: C, 65.50; H, 4.99.

Example 28

[6-Methoxy-2-(4-methoxyphenyl)-3-bromo]benzo[b] thiophene-(S-oxide)

[0199]
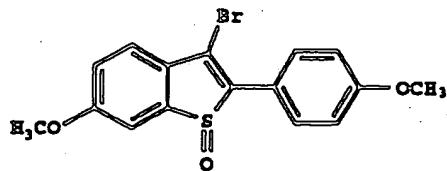
[0200] To a solution of [6-methoxy-2-(4-methoxyphenyl)-3-bromo]benzo [b]thiophene (10.0 g, 28.6 mmol) in 50 mL of anhydrous methylene chloride was added 50 mL of triflouroacetic acid. After stirring for 5 minutes, hydrogen peroxide (4.0 mL, 28.6 mmol, 30% aqueous solution) was added. The resulting mixture was stirred at ambient temperature for 2 hours. Solid sodium bisulfite (1.25 g) was added to the dark solution followed by 15 mL of water. The mixture was stirred vigorously for 15 minutes then concentrated *in vacuo*. The residue was partitioned between chloroform saturated sodium bicarbonate solution (200 mL ea.). The layers were separated and the organic layer was extracted with saturated sodium bicarbonate solution. The organic layer was then dried (sodium sulfate) and concentrated *in vacuo* to a solid that was triturated from ethyl ether/ethyl acetate. Filtration provided 8.20 g (80%) of [6-methoxy-2-(4-methoxyphenyl)-3-bromo]benzo [b]thiophene-(S-oxide) as a yellow solid that can be recrystallized from ethyl acetate. m.p. 170-173° C. ^{1}H NMR (DMSO-d_6) d 7.24 (d, J = 2.2 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.26 (dd, J = 8.5, 2.2 Hz, 1H), 7.10 (d, J = 8.8 H, 2H), 3.86 (5, 3H), 3.80 (s, 3H). *Anal. Calcd.* for $C_{16}H_{13}O_3SBr$: C, 52.62; H, 3.59. Found: C, 52.40; H, 3.55.

Example 29

Prepared in an analogous manner was [2-(4-methoxyphenyl)-3-bromo]benzo[b]thiophene-(S-oxide).

[0201]
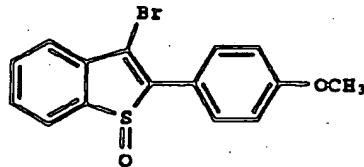
mp 120-125 °C. ^{1}H NMR (DMSO-d_6) d 8.06 (d, J = 7.6 Hz, 1H), 7.78-7.59 (m, 5H), 7.13 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H). FD mass spec: 335. *Anal.* Calcd. for $C_{15}H_{11}O_2SBr$: C, 53.75; H, 3.31. Found: C, 53.71; H, 3.46.

Preparation 12

Preparation of 4-(2-(1-piperidinyl)ethoxy)-phenol.

[0202]
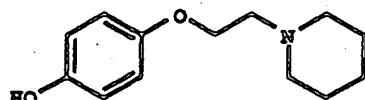
[0203] To a solution of 4-benzyloxyphenol (50.50 g, 0.25 mol) in 350 mL of anhydrous DMF was added 2-chloroethyl-piperidine (46.30 g, 0.25 mol). After stirring for 10 minutes, potassium carbonate (52.0 g, 0.375 mol) and cesium carbonate (85.0 g, 0.25 mol) were added. The resulting heterogeneous mixture was stirred vigorously at ambient temperature for 48 hours. The reaction was then poured into water (500 mL) and extracted with methylene chloride. The organic was then extracted with 1 N sodium hydroxide several times and finally washed with brine. The organic layer was then dried (sodium sulfate) and concentrated *in vacuo* to an oil. Chromatography (SiO$_2$, 1:1 hexanes/ethyl acetate) provided 60.0 g (77%) of 4-[2-(1-piperidinyl)ethoxy]phenoxybenzyl ether as a colorless oil. ^{1}H NMR (DMSO-d_6) d 7.40-7.27 (m, 5H), 6.84 (q, J_{AB} = 11.5 Hz, 4H), 4.98 (s, 2H), 3.93 (t, J = 6.0 Hz, 2H), 2.56 (t, J = 6.0 Hz, 2H), 2.35-2.37 (m, 4H), 1.48-1.32 (m, 6H). FD mass spec: 311. *Anal.* Calcd. for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.34; H, 8.18; N, 4.64.

[0204] 4-[2-(1-Piperidinyl)ethoxy]phenoxybenzyl ether (21.40 g, 68,81 mmol) was dissolved in 200 mL of 1:1 EtOH/EtOAc containing 1% con. HCl. The solution was transferred to a Parr bottle, and 5% palladium-on-carbon (3.4 g) was added. The mixture was hydrogenated at 40 psi for 2 hours. The mixture was then passed through a plug of Celite to remove catalyst. The filtrate was concentrated *in vacuo* to a solid that was slurried in ethyl ether and filtered to provide 12.10 g (83%) of 4-(2-(1-piperidinyl) ethoxy)-phenol. mp 148-150° C. ^{1}H NMR (DMSO-d_6) d 8.40 (s, 1H), 6.70 (q, J_{AB} = 11.5 Hz, 4H), 3.93 (t, J = 6.0 Hz, 2H), 2.59 (t, J = 6.0 Hz, 2H), 2.42-2.38 (m, 4H), 1.52-1.32 (m, 6H). FD mass spec: 221. *Anal.* Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.09; N, 4.50. Found: C, 70.75; H, 8.59; N, 6.54.

Example 30

[6-Methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene-(S-oxide)

[0205]
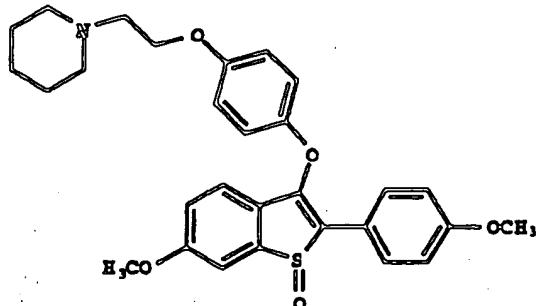
[0206] To a solution of 4-(2-(1-piperidinyl)ethoxy)-phenol (0.32 g, 1.43 mmol) in 5 mL of anhydrous DMF at ambient temperature was added sodium hydride (0.57 g, 1.43 mmol, 60% dispersion in mineral oil). After stirring for 15 minutes, [6-methoxy-2-(4-methoxyphenyl)-3-bromo]benzo[b]thiophene-(S-oxide) (0.50 g, 1.37 mmol) was added in small portions. After stirring for 1 hour, the reaction was judged complete by TLC analysis. The solvent was removed *in vacuo,* and the residue was distributed between water and 10% ethanol/ethyl acetate. The organic was washed several times with water and then dried (sodium sulfate). Concentration *in vacuo* gave an oil that was triturated from ethyl acetate/ hexanes to provide 0.62 g (89%) of [6-methoxy-3-[4-[2-(1-piperidinyl)ethoxy] phenoxy]-2-(4-methoxyphenyl)]benzo[b] thiophene-(S-oxide) as a light yellow solid. mp 97-100° C. ^{1}H NMR (DMSO-d_6) d 7.68 (d, J = 2.1 Hz, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.06-6.92 (m, 6H), 6.85 (d, J = 8.8 Hz, 2H), 3.94 (t, J = 6.0 Hz, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 2.56 (t, J = 6.0 Hz, 2H), 2.39-2.32 (m, 4H), 1.47-1.32 (m, 6H). *Anal.* Calcd. for $C_{29}H_{31}NO_5S$: C, 68.89; H, 6.18; N, 2.77. Found: C, 68.95; H, 6.04; N, 2.57.

Example 31

**Prepared in an analogous manner was [3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)] benzo[b] thiophene-(S-oxide)**

[0207]
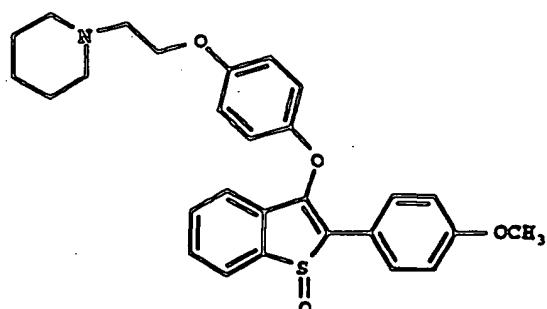
[0208] Oil. ^{1}H NMR (DMSO-d_6) d 8.03 (m, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.53-7.50 (m, 2H), 7.09-6.82 (m, 7H), 3.94 (bt, J = 5.9 Hz, 2H), 3.74 (s, 3H), 2.56 (bt, J = 5.9 Hz, 2H), 2.36-2.33 (m, 4H), 1.45-1.31 (m, 6H). FD mass spec: 475. *Anal.* Calcd. for $C_{28}H_{29}NO_4S$: C, 70.71; H, 6.15; N, 2.94. Found: C, 70.44; H, 6.43; N, 3.20.

Example 32

[6-Methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride

[0209]
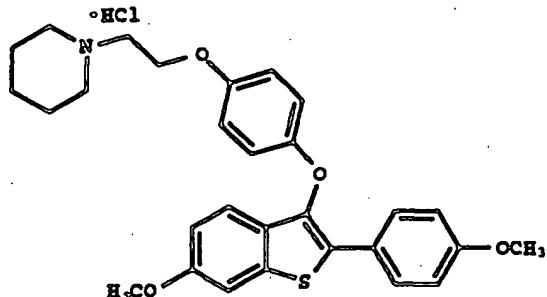
[0210] To a solution of [6-methoxy-3-[4-[2-(1-piperidinyl) ethoxy] phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene-(S-oxide) (Example 30) (3.00 g, 5.94 mmol) in 200 mL of anhydrous THF under nitrogen gas at 0° C was added lithium aluminum hydride (0.34 g, 8.91 mmol) in small portions. After stirring for 30 minutes, the reaction was quenched by the careful addition of 5.0 mL of 2.0 N sodium hydroxide. The mixture was stirred vigorously for 30 minutes, and additional 2.0 N sodium hydroxide was added to dissolve salts. The mixture was then distributed between water and 10% sodium hydroxide. The layers were separated and the aqueous extracted several times with 10% ethanol/ethyl acetate. The organic layer was dried (sodium sulfate) and concentrated *in vacuo* to an oil. The crude product was dissolved in 50 mL of 1:1 ethyl acetate/ethyl ether and treated with excess ethyl ether hydrochloride. The resulting precipitate was collected and dried to provide 2.98 g (96%) of [6-methoxy-3-[4-[2-(1-piperidinyl) ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene hydrochloride as a white solid.

[0211] Example 6 was also prepared from Example 31 by the same procedure.

Preparation 13

6-Methoxybenzo[b]thiophene-2-boronic acid

[0212]
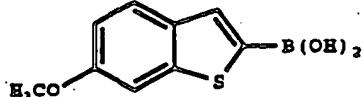
[0213] To a solution of 6-methoxybenzo[b]thiophene (18.13 g, .111 mol) in 150 mL of anhydrous tetrahydrofuran (THF) at - 60° C was added n-butyllithium (76.2 mL, .122 mol, 1.6 M solution in hexanes), dropwise via syringe. After stirring for 30 minutes, triisopropyl borate (28.2 mL, .122 mol) was introduced via syringe. The resulting mixture was allowed to gradually warm to 0° C and then distributed between 1N hydrochloric acid and ethyl acetate (300 mL each). The layers were separated, and the organic layer was dried over sodium sulfate. Concentration *in vacuo* produced a white solid that was triturated from ethyl ether hexanes. Filtration provided 16.4 g (71%) of 6-methoxybenzo[b] thiophene-2-boronic acid as a white solid. mp 200° C (dec). ^{1}H NMR (DMSO-d_6) d 7.83 (s, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 6.97 (dd, J = 8.6, 2.0 Hz, 1H), 3.82 (s, 3H). FD mass spec: 208.

Preparation 14

**[6-Methoxy-2-(4-methanesulfonyloxyphenyl)]benzo[b] thiophene**

[0214]
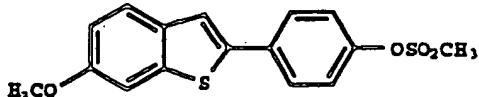
[0215] To a solution of 6-methoxybenzo[b]thiophene-2-boronic acid (3.00 g, 14.4 mmol) in 100 mL of toluene was added 4-(methanesulfonyloxy)phenylbromide (3.98 g, 15.8 mmol) followed by 16 mL of 2.0 N sodium carbonate solution. After stirring for 10 minutes, tetrakistriphenylphosphinepalladium (0.60 g, 0.52 mmol) was added, and the resulting mixture was heated to reflux for 5 hours. The reaction mixture was then allowed to cool to ambient temperature whereupon the product precipitated from the organic phase. The aqueous phase was removed and the organic layer was concentrated *in vacuo* to a solid. Trituration from ethyl ether yielded a solid that was filtered and dried *in vacuo* to provide 3.70 g (77%) of [6-methoxy-2-(4-methanesulfonyloxy-phenyl)]benzo[b]thiophene as a tan solid. mp 197-201° C. ^{1}H NMR (DMSO-d_6) d 7.82-7.77 (m, 3H), 7.71 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 8.7 Hz, 2H), 6.98 (dd, J = 8.7, 1.5 Hz, 1H), 3.80 (s, 3H), 3.39 (s, 3H). FD mass spec 334. *Anal.* Calcd. for $C_{16}H_{14}O_4S_2$: C, 57.46; H, 4.21. Found: C, 57.76; H, 4.21.

Preparation 15

Prepared in an analogous manner to Preparation 14 was [6-methoxy-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[0216]
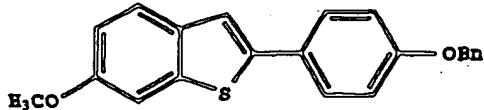
Yield = 73 %. mp 217-221° C. ^{1}H NMR (DMSO-d_6) d 7.63-7.60 (m, 3H), 7.59-7.26 (m, 7H), 7.02 (d, J = 8.7 Hz, 2H), 6.96 (dd, J = 8.8, 2.2 Hz, 1H), 5.11 (s, 2H), 3.88 (s, 3H). FD mass spec 346. *Anal.* Calcd. for $C_{22}H_{18}O_2S$: C, 76.27; H, 5.24. Found: C, 76.00; H, 5.25.

Preparation 16

[6-Hydroxy-2-(4-methanesulfonyloxyphenyl)]benzo[b] thiophene

[0217]
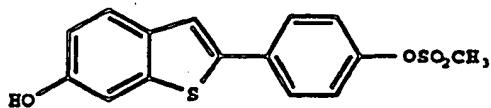
[0218] To a solution of [6-methoxy-2-(4-methanesulfonyloxyphenyl)]benzo[b]thiophene (9.50 g, 28.40 mmol) in anhydrous methylene chloride (200 mL) at room under nitrogen gas was added boron tribromide (14.20 g, 5.36 mL, 56.8 mmol). The resulting mixture was stirred at ambient temperature for 3 hours. The reaction was quenched by slowly pouring into excess ice water. After vigorously stirring for 30 minutes, the white precipitate was collected by filtration, washed several times with water, and then dried *in vacuo* to provide 8.92 g (98%) of [6-hydroxy-2-(4-methanesulfony-loxyphenyl)] benzo[b]thiophene as a white solid. mp 239-243° C. ^{1}H NMR (DMSO-d_6) d 9.70 (s, 1H), 7.76 (d, J = 8.7

Hz, 2H), 7.72 (s, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 1.7 Hz, 1H), 6.86 (dd, J = 8.7, 1.7 Hz, 1H), 3.38 (s, 3H). FD mass spec 320. *Anal.* Calcd. for $C_{15}H_{12}O_4S_2$: C, 56.23; H, 3.77. Found: C, 56.49; H, 3.68.

Preparation 17

[6-Benzyloxy-2-(4-methanesulfonyloxyphenyl)]benzo [b]thiophene

[0219]
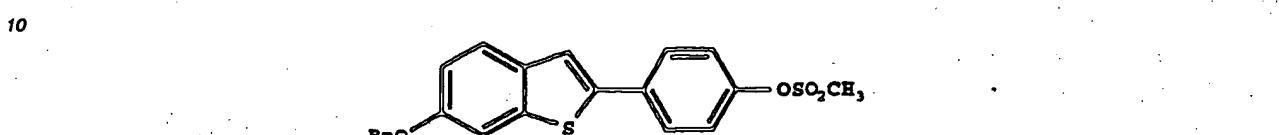
[0220]   To a solution of [6-hydroxy-2-(4-methanesulfonyloxyphenyl)] benzo[b]thiophene (3.20 g, 10.0 mmol) in 75 mL of anhydrous DMF was added Cs_2CO_3 (5.75 g, 17.7 mmol) followed by benzylchloride (1.72 mL, 11.0 mmol). The resulting mixture was stirred vigorously for 24 hours. The solvent was removed *in vacuo*, and the solid residue was suspended in 200 mL of water. The white precipitate was collected by filtration and washed several times with water. Upon drying *in vacuo*, the crude product was suspended in 1:1 hexanes:ethyl ether. The solid was collected to provide 3.72 g (91%) of [6-benzyloxy-2-(4-methanesulfonyloxy-phenyl)]benzo[b]thiophene as a white solid. mp 198-202° C. ^{1}H NMR (DMSO-d_6) d 7.81-7.78 (m, 3H), 7.72 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.47-7.30 (m, 7H), 5.15 (s, 2H), 3.39 (s, 3H). FD mass spec 410.

Preparation 18

[6-Benzyloxy-2-(4-hydroxyphenyl)]benzo[b]thiophene

[0221]
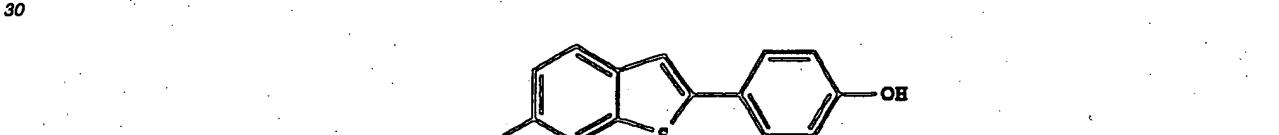
[0222]   To a solution of [6-benzyloxy-2-(4-methanesulfonyloxyphenyl)]benzo[b]thiophene (12.50 g, 30.50 mmol) in 300 mL of anhydrous THF under nitrogen gas at ambient temperature was added lithium aluminum hydride (2.32 g, 61.0 mmol) in small portions. The mixture was then stirred at ambient temperature for 3 hours and then quenched by carefully pouring the mixture into an excess of cold 1.0 N hydrochloric acid. The aqueous phase was extracted with ethyl acetate. The organic was then washed several times with water and then dried (sodium sulfate) and concentrated *in vacuo* to a solid. Chromatography (silicon dioxide, chloroform) provided 8.75 g (87%) of [6-benzyloxy-2-(4-hydrox-yphenyl)]benzo[b] thiophene as a white solid. mp 212-216° C. ^{1}H NMR (DMSO-d_6) d 9.70 (s, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.51-7.30 (m, 8H), 7.00 (dd, J = 8.7, 2.2 Hz, 1H), 6.80 (d, J = 8.6 Hz, 2H), 5.13 (s, 2H). FD mass spec 331. *Anal.* Calcd. for $C_{21}H_{16}O_2S$: C, 75.88; H, 4.85. Found: C, 75.64; H, 4.85.

Example 19

**[6-Benzyloxy-2-(4-methoxyphenyl)]benzo[b]thiophene**

[0223]
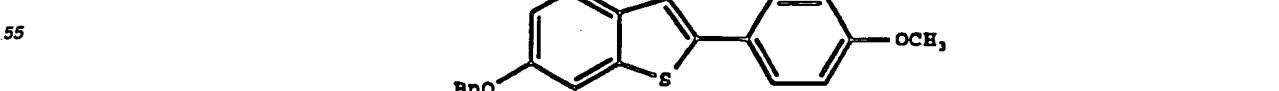
[0224] To a solution of [6-benzyloxy-2-(4-hydroxyphenyl)] benzo[b] thiophene (8.50 g, 26.40 mmol) in 200 mL of anhydrous DMF under nitrogen gas at ambient temperature was added sodium hydride (1.66 g, 41.5 mmol) in small portions. Once gas evolution had ceased, iodomethane (3.25 mL, 52.18 mmol) was added dropwise. The reaction was stirred for 3 hours at ambient temperature. The solvent was then removed *in vacuo,* and the residue distributed between water/ethyl acetate. The layers were separated, and the organic phase was washed several times with water. The organic layer was then dried (sodium sulfate) and concentrated *in vacuo* to provide 9.00 g (98%) of [6-benzyloxy-2-(4-methoxyphenyl)] benzo[b]thiophene as a white solid. mp 180-185° C. ^{1}H NMR (DMSO-d_6) d 7.67-7.58 (m, 5H), 7.46-7.29 (m, 5H), 7.02 (dd, J = 8.8, 2.2 Hz, 1H), 6.98 (d, J = 8.7 Hz, 2H), 5.13 (s, 2H), 3.76 (s, 3H). FD mass spec 346. *Anal.* Calcd. for $C_{22}H_{18}O_2S$: C, 76.27; H, 5.24. Found: C, 76.54; H, 5.43.

Preparation 20

**[6-Benzyloxy-2-(4-methoxyphenyl)-3-bromo]benzo-[b]thiophene**

[0225]
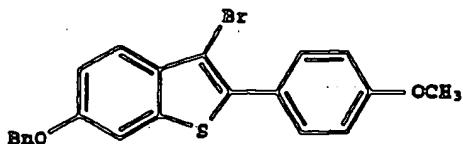
[0226] [6-Benzyloxy-2-(4-methoxyphenyl)]benzo[b]thiophene (10.0 g, 28.9 mmol) was placed in 200 mL of chloroform along with 10.0 g of solid sodium bicarbonate at ambient temperature. To this suspension was added bromine (1.50 mL, 29.1 mmol) dropwise over 30 minutes as a solution in 100 mL of chloroform. Upon completion of the addition, water (200 mL) was added and the layers were separated. The organic phase was dried (sodium sulfate) and concentrated *in vacuo* to a white solid. Crystallization from methylene chloride/ methanol provided 10.50 g (85%) of [6-benzyloxy-2-(4-methoxyphenyl)-3-bromo]benzo-[b]thiophene as a white solid. mp 146-150° C. ^{1}H NMR (DMSO-d_6) d 7.70 (d, J = 2.2 Hz, 1H), 7.65-7.60 (m, 3H), 7.47-7.30 (m, 5H), 7.19 (dd, J = 8.8, 2.2 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 5.17 (s, 2H), 3.78 (s, 3H). FD mass spec 346. *Anal.* Calcd. for $C_{22}H_{17}O_2SBr$: C, 62.13; H, 4.03. Found: C, 61.87; H, 4.00.

Preparation 21

**Prepared in an analogous manner was [6-methoxy-2-(4-benzyloxyphenyl)-3-bromo]benzo-[b]thiophene**

[0227]
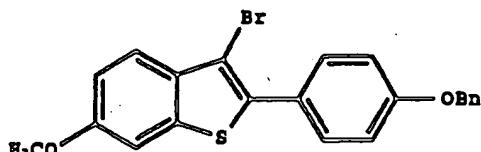
Yield = 91%. mp 125-127° C. ^{1}H NMR (DMSO-d_6) d 7.64-7.61 (m, 4H), 7.46-7.31 (m, 5H), 7.15-7.09 (m, 3H), 5.15 (s, 2H), 3.82 (s, 3H). FD mass spec 346. *Anal.* Calcd. for $C_{22}H_{17}O_2SBr$: C, 62.13; H, 4.03. Found: C, 62.33; H, 3.93.

Prepared in a manner analgous to Example 28 are Examples 33-34.

Example 33

[6-Benzyloxy-2-(4-methoxyphenyl)-3-bromo]benzo[b] thiophene-(S-oxide)

[0228]
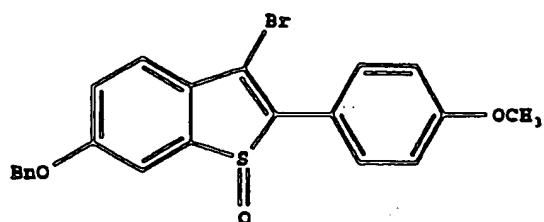
[0229]   Isolated as a yellow solid by crystallization from ethyl acetate. mp 202-205° C. ^{1}H NMR (DMSO-d_6) d 7.80 (d, J = 2.2 Hz, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.55(d, J = 8.4 Hz, 1H) 7.47-7.32 (m, 6H), 7.10 (d, J = 8.7 Hz, 2H), 5.23 (s, 2H), 3.80 (s, 3H). FD mass spec 441. *Anal.* Calcd. for $C_{22}H_{17}O_3SBr$: C, 59.87; H, 3.88. Found: C, 59.59; H, 3.78.

Example 34

[6-Methoxy-2-(4-benzyloxyphenyl)-3-bromo]benzo[b] thiophene-(S-oxide)
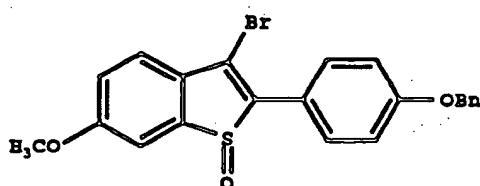
[0230]

[0231]   Isolated as a yellow solid by chromatography (SiO$_2$, CHCl$_3$). mp 119-123° C. ^{1}H NMR (DMSO-d_6) d 7.73 (d, J = 2.2 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.5 Hz, 1H) 7.46-7.31 (m, 5), 7.26 (dd, J = 8.5, 2.2 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 5.16 (s, 2H), 3.86 (s, 3H). FD mass spec 441. *Anal.* Calcd. for $C_{22}H_{17}O_3SBr$: C, 59.87; H, 3.88. Found: C, 60.13; H, 4.10.

[0232]   Prepared in a manner analagous to Example 30 are Examples 35-36.

Example 35

[6-Benzyloxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene-(S-oxide)

5   **[0233]**
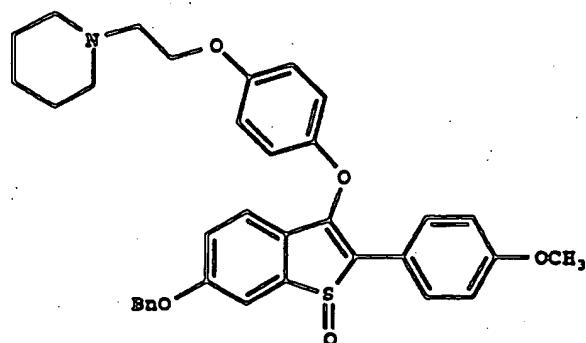
20

[0234] Yellow oil. ^{1}H NMR (DMSO-d_6) d 7.76 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.44-7.30 (m, 5H), 7.12 (dd, J = 8.6, 2.2 Hz, 1H), 7.03-6.93 (m, 5H), 6.85 (d, J = 8.8 Hz, 2H), 5.18 (s, 2H), 3.94 (bt, J = 5.8 Hz, 2H), 3.73 (s, 3H), 2.56 (bt, J = 5.8 Hz, 2H), 2.37-2.34 (m, 4H), 1.45-1.32 (m, 6H). FD mass spec 592. *Anal.* Calcd. for $C_{35}H_{35}NO_5S$: C, 72.26; H, 6.06; N, 2.41. Found: C, 72.19; H, 5.99; N, 2.11.

Example 36

[6-Methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene-(S-oxide)

30   **[0235]**
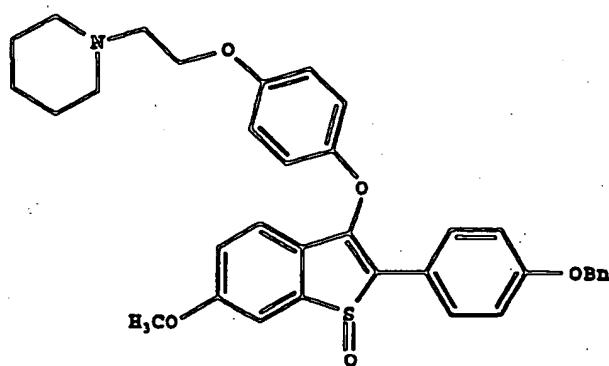
45

[0236] Yellow solid. mp 89-93° C. ^{1}H NMR (DMSO-d_6) d 7.68 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.42-7.28 (m, 5H), 7.08-6.92 (m, 6H), 6.86 (d, J = 8.8 Hz, 2H), 5.09 (s, 2H), 3.94 (bt, J = 5.8 Hz, 2H), 3.81 (s, 3H), 2.56 (bt, J = 5.8 Hz, 2H), 2.37-2.34 (m, 4H), 1.45-1.31 (m, 6H). FD mass spec 592. *Anal.* Calcd. for $C_{35}H_{35}NO_5S$°0.25 EtOAc: C, 71.62; H, 6.18; N, 2.32. Found: C, 71.32; H, 5.96; N, 2.71.

[0237] Prepared in a manner analagous to Example 11 are Exampes 37-38.

Example 37

[6-Benzyloxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-methoxyphenyl)]benzo[b]thiophene

[0238]
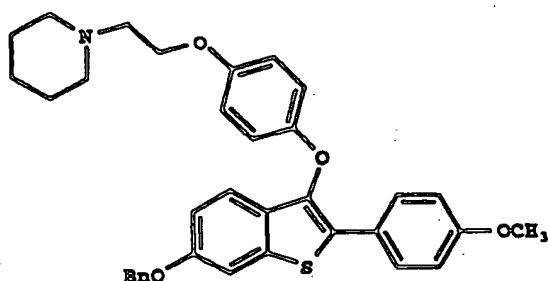
[0239]   Isolated in 95% overall yield starting from [6-benzyloxy-2-(4-methoxyphenyl)-3-bromo]benzo[b]thiophene-(S-oxide). Purified by chromatography (SiO$_2$, 1-5% methanol/chloroform) to provide an off-white solid. mp 105-108° C. ^{1}H NMR (DMSO-d_6) d 7.62 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.45-7.30 (m, 5H), 7.15 (dd, J = 8.6 Hz, 1H), 7.00-6.94 (m, 3H), 6.82 (s, 4H), 5.13 (s, 2H), 3.92 (bt, J = 5.8 Hz, 2H), 3.72 (s, 3H), 2.55 (bt, J = 5.8 Hz, 2H), 2.37-2.34 (m, 4H), 1.44-1.31 (m, 4H). FD mass spec 565. *Anal.* Calcd. for C$_{35}$H$_{35}$NO$_4$S: C, 74.31; H, 6.24; N, 2.48. Found: C, 74.35; H, 6.07; N, 2.76.

Example 38

[6-Methoxy-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]-2-(4-benzyloxyphenyl)]benzo[b]thiophene

[0240]
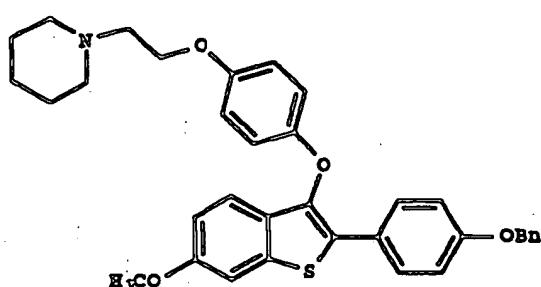
[0241]   Yield = 91%. mp 106-110° C. ^{1}H NMR (DMSO-d_6) d 7.59 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 2.2 Hz, 1H), 7.42-7.28 (m, 5H), 7.13 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.82 (s, 4H), 5.08 (s, 2H), 3.92 (bt, J = 5.8 Hz, 2H), 3.78 (s, 3H), 2.55 (bt, J = 5.8 Hz, 2H), 2.37-2.33 (m, 4H), 1.44-1.31 (m, 4H). FD mass spec 565. *Anal.* Calcd. for C$_{35}$H$_{35}$NO$_4$S: C, 74.31; H, 6.24; N, 2.48. Found: C, 74.26; H, 6.17; N, 2.73.